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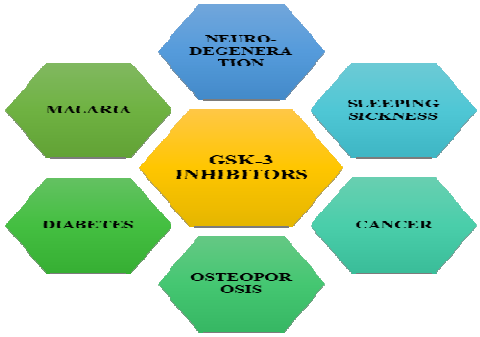

Glycogen synthase kinase-3 and its inhibitors: Potential target for various therapeutic conditions.

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1. Introduction

Glycogen Synthase Kinase-3 (GSK-3) is a serine/threonine protein kinase often referred as a "multitasking kinase" due to its versatile role in various signalling pathways [1-3]. It belongs to the class of kinases that come under the family of phosphotransferases. Initially, it was known to regulate glycogen synthase, but today it is known to phosphorylate broad range of substrates regulating several biological processes. GSK-3 is involved in various cellular events like Wnt, Hedgehog signalling pathways, neuronal development, transcription, insulin pathway, cell division, cell survival and cell death etc. [4-6]. Due to its multifarious applications in various cellular events, any aberrant activity of GSK-3 leads to variety of disorders including Alzheimer's [7, 8], cancer [9-11], diabetes [12], cardiovascular disorders [13, 14], neurodegeneration [15] and psychiatric disorders [16]. Therefore, GSK-3 is one of the favourable targets being explored in the treatment of these disorders [17].

Glycogen synthase kinase-3, belongs to the CMCG family of proline-directed kinases comprising cyclin-dependent kinases(CDKs), mitogen-activated protein kinases(MAPKs), glycogen synthase kinases(GSKs) and CDK-like kinases (CLKs) [18]. It exists in two isoforms i.e., GSK-3α and GSK-3β which are highly conserved kinases that encode 51 and 47 kDa proteins respectively. GSK-3α and GSK-3β are derived from two GSK-3 genes. Interestingly, GSK-3β exists as longer splice variants also [19, 20]. Both GSK-3α and GSK-3β proteins occurs in many tissues with maximum levels found in the brain. Its activity is found to be high in resting cells and known to inactivate various substrates through phosphorylation with high substrate specificity. GSK-3α and GSK-3β has 98% sequence identity in their kinase domains and 36% identity in their carboxyl termini. However, GSK-3α isoform has an extra feature i.e. a glycine-rich extension at its amino terminus. GSK-3β is regulated by post-translational phosphorylation of Ser9 (inhibitory) and Tyr216 (activating) whereas in case of GSK-3α it is Ser21 and Tyr279, respectively [21]. Significant research

advancements in the area of GSK-3 through animal models and/or cellular studies has provided deep insight about the functional aspects of GSK-3 [18]. Moreover, crystal structure of GSK-3β has also aided in the development of several GSK-3 inhibitors with diverse therapeutic potential [22, 23].

Looking back, lithium salt was the first pharmacological inhibitor of GSK-3 which directly binds to the enzyme and has been used in the treatment of bipolar disorders [24, 25]. Effects on lithium on cell signalling has been widely established [26]. Recently it was found that lithium can also inhibit GSK-3 (*in vivo)* by regulating other mechanisms [27]. Based on the mechanism by which GSK-3 inhibitors acts, they have been classified as ATP-competitive, non ATP-competitive and substrate competitive inhibitors [28]. Natural products have always been a major source for newer drugs [29, 30] and some of them like indirubins, meridianins, manzamines and furanosesquiterpenes that are isolated from marine sources are reported to possess GSK-3 inhibitory properties [31]. The relevance of GSK-3 inhibitors in the area of medicinal chemistry can be understood by the numerous patents which have been filed over the years [32-34]. In recent years, with the emergence of computational tools such as virtual screening, molecular modelling etc., lead identification as well as optimization processes have been impressively improved. This holds true in case of drug discovery in relation to GSK-3 inhibitors as well. The present review focuses on the recent developments in the area of GSK-3 inhibitors with focus on various disorders in which GSK-3 plays a vital role.

1.1. GSK-3 inhibitors under clinical investigation

Several GSK-3 inhibitors are currently undergoing clinical trials for various disorders ***(Figure 1)*** which indicates the multi-functionality of GSK-3 [28, 35]. Tideglusib is under Phase 2 trials for the treatment of mild to moderate progressive supranuclear palsy (PSP). It was subjected to a Tau restoration study (TAUROS) which enrolled a total of 146 PSP

patients with mild-to-moderate disease who were subsequently randomized to receive once-daily a dose of 600 mg tideglusib, 800 mg tideglusib, or placebo (ratio, 2:2:1) administered orally over 52 weeks. Tideglusib was found to be safe, but showed some transient, asymptomatic, and reversible transaminase elevations in 9% of patients as well as diarrhoea in 13% of patients. It was well tolerated but failed to show any clinical efficacy in patients with mild-to-moderate PSP [36]. In another case, Phase IIa study of Tideglusib for the treatment of Alzheimer's disease (AD) was conducted. A total of 30 mild-moderate AD patients being treated with cholinesterase inhibitor were administered escalating doses (400, 600, 800, 1,000 mg) of Tideglusib or placebo for 4, 4, 6, and 6 weeks, respectively. The treatment was well tolerated and the adverse effects were as frequent in active and placebo groups, with exception for some moderate, asymptomatic, and fully reversible increases of serum transaminases in 6 active cases ($p = 0.001$) [37]. A Phase 1 study of oral Enzastaurin in combination with Bevacizumab in patients with advanced/metastatic cancer was conducted. 67 patients (31, ovarian cancer) were evaluated for safety and efficacy. 6 treatment-related DLTs (Dose Limiting Toxicity) occurred which revealed grade 3 fatigue (n=4), grade 4 cerebral haemorrhage, and grade 3 elevated aspartate transaminase. Some common drug-related toxicities were: change in urine and stool colour, nausea pain, fatigue and diarrhoea. The maximum tolerated dose of Enzastaurin was found to be 750 mg BID in combination with any tested bevacizumab dose/schedule. The recommended phase II doses of Enzastaurin were 500 mg QD up to 500 mg BID with any tested dose/schedule of bevacizumab with the combination demonstrating encouraging clinical activity especially in ovarian cancer [38]. In a Phase II study, safety and efficacy of lithium carbonate (0.5-0.8 milliequivalents per liter) was assessed in patients with Machado-Joseph disease (spinocerebellar ataxia type 3 [MJD/SCA3]). 62 patients with MJD/SCA3 with a disease duration less $\leq$ 10 year and an independent gait were assigned (1:1) randomly to receive either lithium or placebo. After 24

weeks, a total of 169 adverse events were reported. To further assess the efficacy, 60 patients were analyzed. Lithium was found to be safe and well tolerated [39].

In addition, 6-BIO (indirubins), hymenialdisine, paullones, arylindolemaleimides, and L803-mts are under preclinical studies.

2. Compounds exhibiting GSK-3 inhibitory activity

2.1. Maleimide derivatives

Maleimide structural motif is abundant in a wide range of natural products that are obtained from both land as well as marine sources [40-42]. Natural products containing this moiety have been reported to possess various biological activities including GSK-3 inhibitory activity (Figure 2). In view of this, Zhang and co-workers synthesized a series of 3-(7-azaindolyl)-4-arylmaleimides as selective inhibitors of GSK-3. Compounds **1** and **2** were found to be the most potent inhibitors among the series demonstrating IC_{50} 0.007 and 0.026 µM respectively. Both the compounds demonstrated very good selectivity over PKC-βII i.e. 325 and >385-fold, respectively. Moreover, these compounds were further tested for their capability to increase glycogen synthase (GS) activity in HEK293 cells which is a direct functional assay to measure GSK-3 inhibitors cellular activity. The results indicated that these compounds effectively block GSK-3β and increased GS activity [43]. In another work, the same group synthesized a series of bis(indolyl)maleimide pyridinophanes as selective inhibitors of GSK-3 and compound **3** was found to be the most active inhibitor of GSK-3 with IC_{50} of 0.003 µM. The biological activity of the compounds was determined with a stress on *in vitro* kinase inhibition. Assays were performed by screening the target compounds against an Upstate panel consisting of 100 kinases (KinaseProfiler^{TM} service) and determining their ability to cause inhibition of phosphorylation of the suitable peptide/protein substrates at a concentration of 1 µM compound and 10 µM ATP. Among all the kinases,

GSK-3 was the most prominently targeted kinase and the compounds demonstrated excellent selectivity except for MSK1, PKCϴ and Rsk1-3 [44]. Continuing their research in this area, the same group reported dual GSK-3 and Protein Kinase C inhibitory activity of a series of macrocyclic bisindolylmaleimides and in this series, compound **4** was found to be the most potent molecule exhibiting an IC_{50} of 0.004 µM. The compounds were tested for their cellular activity using a direct functional assay, wherein their ability to increase glycogen synthase (GS) activity in HEK293 cells is measured. The results indicated effective GSK-3β blockade and increased GS activity within the cells. Compound **4** showed an EC_{50} of 0.31 µM in the conducted assay. Moreover, **4** demonstrated a high selectivity in a screening panel of 10 other kinases. Overall, the compounds exhibited a good selectivity over PKC-α, -γ, -δ, -ε, and –ζ and were effective intracellularly in blocking PKC-βII-induced IL-8 release and increasing glycogen synthase activity [45].

Similarly, Ye and co-workers developed a series of 4-azaindolyl-indolyl-maleimides as GSK-3β inhibitors and the most potent compound **5** exhibited an IC_{50} of 0.14 µM. Moreover, compound **5** significantly decreased Aβ-induced *tau* hyperphosphorylation by inhibiting GSK-3β. A cell-based assay examining Tau phosphorylation at Ser396 which represents a direct functional assay was conducted to measure the cellular activity of GSK-3 inhibitors. Selected compounds were tested for their potential to reduce Tau phosphorylation at Ser396 in human neuroblastoma SH-SY5Y cells. With regard to the selectivity, some of the compounds demonstrated high selectivity against PKCE, IKK2, Aurora A, MEK1 and ERK1 [46]. In another work, the same group synthesised a series of 7-azaindazolyl-indolyl maleimides as GSK-3β inhibitors. Compound **6** was found to exhibit promising activity with an IC_{50} 0.36 µM. It also significantly reduced Aβ-induced tau hyperphosphorylation, inhibiting GSK-3β at the cellular level. The cellular activity was measured using a cell-based assay examining Tau phosphorylation at Serine 396 as seen in their previous work. The

compounds were tested for their capability to reduce Tau phosphorylation at Ser396 in human neuroblastoma SH-SY5Y cells. Selectivity of compounds was determined using Invitrogen Z'-LYTETM Kinase Assay kits. Based on the results, certain compounds displayed inhibitory activities against PKCE, IKK2, Aurora A, MEK1 and ERK1. The results showed that some of the tested compounds exhibited high selectivity for GSK-3β over other tested kinases [47].

In the same way, O'Neill and co-workers reported a series of 7-azaindolyl heteroaryl-maleimides as selective GSK-3β inhibitors and compound **7** exhibits IC_{50} of 0.025 μM. In order to measure the cellular activity the compounds were tested for their ability to increase GS activity in human embryonic kidney (HEK293) cells. Also, the tested compounds displayed acceptable metabolic stability in human liver microsomes. The selectivity of compounds was determined against a broad panel of 80 protein kinase assays at UBI (Upstate Biotech Inc.). Among the tested compounds, **7** exhibited very weak inhibitions over the other 79 kinase assays, and emerged as a highly selective GSK-3β inhibitor [48]. Shen and co-workers synthesised a series of macrocyclic bis-7-azaindolylmaleimides and evaluated for GSK-3β inhibitory activity. Compound **8** was found to be most effective from the series, inhibiting GSK-3β with IC_{50} 0.011 μM. The cellular activity was measured *via* a direct functional assay which examines the increase in GS activity in human embryonic kidney (HEK293) cells. To determine the selectivity of the compounds they were subjected to UBI (Upstate Biotech Inc.) for broad screening against a panel of 66 protein kinases. Some of the compounds exhibited twice the magnitude of selectivity at GSK-3β against CDK2, PKCβII, Rsk3 and mild or no inhibitions versus 62 other protein kinases. Compound **8** demonstrated a 100-fold greater selectivity at GSK-3 versus a panel of 65 protein kinases and stood out as a GSK-3β 'specific inhibitor' [49]. In analogy, Kuo and co-workers developed macrocyclic polyoxygenated bis-7-azaindolylmaleimides as selective GSK-3β inhibitors. In this series,

compound **9** effectively inhibited GSK-3β activity with an IC_{50} of 0.017 μM. A direct functional assay which measures the increase in GS activity was employed as a method to determine cellular activity of GSK-3 inhibitors. Compounds were tested for their ability to increase the activity of glycogen synthase in human embryonic kidney cells, HEK293. Kinase selectivity was determined against a panel of kinases like CDK, PKC isoenzymes and other ATP-dependent kinases namely PKA, calmodulin K, and casein K. The compounds exhibited little or no inhibitions to 50 protein kinase panel [50]. On the other hand, Engler and co-workers synthesised a series of bisarylmaleimides and tested them for GSK-3 inhibition potential and the most potent compound **10** amongst the series displayed IC_{50} of 0.0007 μM. To determine the cellular activity, they relied on a cell-based assay which measured the inhibition of Ser396 phosphorylation of tau which is a natural substrate of GSK3 in SY5Y cells. The compounds were also effective in plasma glucose lowering in Zucker diabetic fatty (ZDF) rats which are an established animal model for type 2 diabetes. Moreover, the compounds were found to be highly selective (>160 to >10,000-fold) versus CDK2/4 and PKCβII [51]. Similarly, Gunosewoyo and co-workers reported benzofuran-3-yl-(indol-3-yl)maleimides as GSK-3β inhibitors which stimulate steroidogenesis. From this series of compounds, **11** and **12** successfully stimulated progesterone production in the MA-10 mouse tumour Leydig cell model of steroidogenesis without showing any significant toxicity. Also, on testing the two compounds in the SmartCube behavioural assay, they showed anxiolytic-like signatures on administration of daily dose 50 mg/kg, ip for 13 days. IC_{50} values of **11** and **12** were 0.0211 and 0.0198 μM respectively [52]. In contrast, Schmöle and co-workers synthesised a series of unsymmetrically substituted indolylmaleimides as GSK-3β inhibitors that have been investigated in human neural progenitor cell line. Among these, **13** was found to be most active with IC_{50} of 0.053 μM. The compounds were tested for

their ability as activators of canonical Wnt signalling using ELISA test assay. Further treatment of human progenitor cells with **13** resulted in the increase of neuronal cells [53].

2.2. Pyridine and pyrimidine derivatives

Pyridine and pyrimidine are widely abundant nitrogen heterocycles which have been highly exploited to develop potential GSK-3 inhibitors (Figure 3). Pyridine is one of the most important heterocycle used to develop bioactive agents [54]. In this regard, Witherington and co-workers synthesized a series of 5-aryl-pyrazolo[3,4-*b*]pyridines and tested their GSK-3 inhibitory activity, wherein **14** was found to be the most potent compound exhibiting an IC_{50} value of 0.005 µM. The compounds were tested against a panel of more than 20 kinases including GSK-3β. Excellent selectivity was observed against all kinases however significant inhibition of CDK2 was observed [55]. The same group reported a series of 6-aryl-pyrazolo[3,4-*b*]pyridines as GSK-3 inhibitors, and the most potent compound **15** amongst the series exhibited an IC_{50} value of 0.001 µM [56]. Further continuing their work, they developed a series of 6-heteroaryl-pyrazolo[3,4-*b*]pyridines as GSK-3 inhibitors, wherein compound **16** exhibited excellent GSK-3 inhibitory activity displaying an IC_{50} value of 0.0008 µM [57]. Similarly, Chun and co-workers came up with a series of 8-amino-[1,2,4]triazolo[4,3-*a*]pyridin-3(2H)-one derivatives that inhibit GSK-3 and in this series, the most potent compound **17** exhibited an IC_{50} value of 0.111 µM and desirable oral PK and water solubility. H4IIE (ATCC, CRL154) was employed for the cell-based assay and the results were obtained using commercially available human recombinant GSK-3 enzyme and phosphor-glycogen synthase-2 peptide. The off-target screening results showed that inhibition percentages of **17** against CDK2 and CDK5 were 54% and 53% respectively at a concentration of 10 µM [58]. In another work, Sivaprakasam and co-workers reported a series of new acylaminopyridine compounds with various central spacers as potent GSK-3β inhibitors. Among these, **18** from the thiazolylpyridine series significantly lowered

phosphorylated Tau levels at Ser396, when administered orally in a triple transgenic AD mouse model. Competitive binding assays of the compounds were carried out in order to evaluate their ability to bind and inhibit the activity of GSK-3β. **18** demonstrated an IC_{50} value of 0.29 nM [59].

Pyrimidine nucleus is commonly found in chemical agents targeting diverse biomolecules [60-62]. In view of this, Lum and co-workers developed a series of 2,5-diaminopyrimidines and 3,5-disubstituted azapurines as inhibitors of GSK-3. Amongst them, **19** was found to be the most potent compound with IC_{50} 0.0045 and 0.003 µM against GSK-3α and GSK-3β respectively. Optimization of these compounds led to inhibitors with IC_{50} < 0.01 µM and > 0.1-fold selectivity over Aurora A kinase. Assays for GSK-3 and Aurora A kinase inhibition were carried out using Z'lyte reagents (Invitrogen) [63]. Similarly, Maeda and co-workers synthesized a series of 4-acylamino-6-arylfuro[2,3-*d*]pyrimidines and tested their potential towards selective inhibition of GSK-3. In this series, **20** was found to be the most promising candidate with an IC_{50} of 0.005 µM. The hGSK-3β enzyme assay was performed using scintillation proximity assay (SPA). [64]. In analogy, Miyazaki and co-workers reported 4-amino-5,6-diaryl-furo[2,3-d]pyrimidines as GSK-3 inhibitors and **21** was found to be the most potent amongst the series with an IC_{50} of 0.03 µM. GSK-3β inhibitory activity was carried out using a fluorescence anisotropy binding assay [65]. Similarly, Smalley and co-workers synthesized a series of pyrimidyl hydrazones as GSK-3 inhibitors and the most potent compound **22** effectively inhibited GSK-3 with IC_{50} of 0.0062 µM. GSK-3 assay was carried out using scintillation proximity assay (SPA) [66].

2.3. Miscellaneous

Arnost and co-workers developed 3-aryl-4-(arylhydrazono)-1*H*-pyrazol-5-ones as GSK-3β inhibitors with high ligand efficiency and compound **23** effectively inhibited GSK-3β with an IC_{50} of 0.0004 µM [67]. In the same way, Witherington and co-workers reported GSK-3

inhibitory activity of 5-aryl-pyrazolo[3,4-b]pyridazines and the most potent compound in the series, **24** displayed excellent activity with an IC_{50} of 0.004 µM [68]. Similarly, Peat and co-workers synthesized a series of [1-(1*H*-benzimidazol-7-yl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl] derivatives and evaluated for their activity against GSK-3. Compound **25** was found to be **t**he most active that exhibited IC_{50} of 0.0062 µM. GSK-3 inhibition assay was carried out using scintillation proximity assay (SPA) [69]. On the other hand, Zou and co-workers synthesized a series of benzo[*e*]isoindole-1,3-diones and tested for their GSK-3 inhibitory property and compound **26** was found to be the most active exhibiting an IC_{50} of 0.270 µM. *In vitro* inhibitory activity against GSK-3β was measured using ELISA assay while the *in vivo* activity was determined using zebra fish embryos [70]. Gentile and co-workers came up with a series of 5-aryl-4-carboxamide-1,3-oxazoles as selective inhibitors of GSK-3. One of the compounds from this series, **27** was found to be excellent inhibitor of GSK-3 that exhibited an IC_{50} value of less than 0.0046 µM [71]. Moreover, Palomo and co-workers reported a series of 5-imino-1,2,4-thiadiazoles as substrate competitive GSK-3 inhibitors and **28** was found to be the most effective compound from this series displaying an IC_{50} of 0.3 µM [72]. Similarly, Shin and co-workers developed a series of 7-hydroxy-1*H*-benzoimidazole derivatives as GSK-3β inhibitors and the most potent compound **29** exhibited an IC_{50} of 0.015 µM [73]. Testard and co-workers synthesized a series of thiazolo[5,4-*f*]quinazolin-9-ones and tested for their GSK-3 inhibitory activity, wherein compound **30** was found to be most potent amongst them with an IC_{50} of 0.56 µM [74].

Olesen and co-workers developed a series of 1-(4-aminofurazan-3-yl)-5-dialkylaminomethyl-1H-[1,2,3]triazole-4-carboxylic acid derivatives as selective inhibitors of GSK-3. The compounds were found to be water soluble and found to be ATP competitive inhibitors. The compounds were tested in a GSK-3 inhibition assay at 100 µM ATP giving IC_{50}'s in the range from 0.1 to 10 µM. The most potent compound **31** exhibited an IC_{50} of 0.28 µM. GSK-

3 inhibition was evaluated using human GSK-3β [75]. Similarly, Cociorva and co-workers synthesised 4-quinolone-3-carboxylic acid based inhibitors of GSK-3β. Compound **32** exhibited remarkable GSK-3 inhibition demonstrating IC_{50} as low as 0.012 μM. GSK-3β assay was carried out using recombinant full-length human GSK-3β (Upstate) [76]. In another work, Koryakova and co-workers reported a series of aryl and heteroaryl substituted *N*-[3-(4-phenylpiperazin-1-yl) propyl]-1,2,4-oxadiazole-5-carboxamides as selective GSK-3 inhibitors, wherein **33** and **34** were found to be potent compounds from this series that inhibit GSK-3 with IC_{50} values of 0.35 and 0.41 μM, respectively. *In vitro* GSK-3β inhibition potency was measured in the ADP Hunter assay [77]. Also, Yue and co-workers reported a series of benzo[e]isoindole-1,3-dione derivatives as selective GSK-3β inhibitors which show high selectivity against GSK-3β over Cyclin-dependent kinase 2 (CDK2) in addition activating the cellular Wnt/β-catenin pathway. Among them, **35** was the most active and selective as it inhibited GSK-3β at IC_{50} 0.34 μM while exhibiting no significant inhibition against CDK2 (3.4% inhibition at 100 μM). Compounds were evaluated for their *in vitro* inhibitory activity against GSK-3β and CDK2 by using Kinase Glo® Luminescent Kinase Assay (Promega) [78]. In a recent work, Arfeen and co-workers synthesised iminothiazolidin-4-one derivatives as selective GSK-3β inhibitors using substituted thiourea, 2-bromoacetophenones and benzaldehydes. Among them, most of the compounds exhibited GSK-3 inhibitory activity in nano-molar range (2-85 nM) in an *in vitro* evaluation. Also, *in vitro* evaluation against CDK-2 confirmed their selectivity towards GSK-3. **36** was found to be the most potent compound with an IC_{50} value of 2.1 nM with CDK-2 residual activity of 73.01% [79].

From the reports summarized above it is evident that a large number of molecules (Figure 4) exhibit excellent activity against GSK-3 which is implicated in a number of human diseases and disorders. Therefore, considering these facts a number of researchers have investigated

the effect of GSK-3 inhibitors for different disease conditions and thus their therapeutic applications are discussed below.

3. Applications of GSK-3 inhibitors

3.1. GSK-3 Inhibitors as anti-Alzheimer's agents

Alzheimer's disease is the most common form of dementia in old age that causes problems with memory, thinking and behaviour. It is characterised by the presence of two abnormal proteins: amyloid plaques and neurofibrillary tangles, caused due to the accumulation of tau hyper-phosphorylation. Tau is a soluble microtubule binding protein which helps in microtubule stabilization in axons [80]. GSK-3β is involved in the formation of paired helical filament (PHF)-tau, which is an integral part of the neurofibrillary tangle deposits that disrupt neuronal function and a marker of neurodegeneration in Alzheimer's disease [7, 81]. Hence, targeting GSK-3 is presumed to be a useful strategy to combat Alzheimer's, due to its involvement in the pathogenesis of this disease. Treatment of patients suffering from Alzheimer's disease with lithium has been widely studied [82]. Currently, many GSK-3 inhibitors are in the pipeline for the treatment of Alzheimer's disease that could provide significant support to the existing drugs used in its treatment [8, 83, 84].

Inspired by the versatile nature of oxadiazole moiety (Figure 6) and other five membered heterocycles [85], Monte and co-workers have synthesized some new oxadiazole based GSK-3 inhibitors and studied their α/β selectivity. Furthermore, the *in vivo* efficacy has been evaluated using zebrafish embryos. Interestingly, compounds displayed selective inhibition of GSK-3α compared to GSK-3β. Compounds **37** and **38** were found to be most promising candidates from this series exhibiting IC_{50} values of 0.006 and 0.316 µM; 0.002 and 0.185 µM against GSK-3α and GSK-3β respectively. *In vitro* GSK-3β inhibitory activity was evaluated by Z'-LYTE technology using human recombinant GSK-3α or GSK-3β as the

enzyme source. [86]. In another work, the same group have reported GSK-3 inhibitory properties of similar compounds without changing the oxadiazole pharmacophore. The acetamide **39** and the benzodioxane **40** caused excellent inhibition of both GSK-3α and GSK-3β with superior selectivity towards the former. This is evident from their IC_{50} values 0.002 µM and 0.035 µM respectively for GSK-3α inhibition [87]. In the same way, Saitoh and co-workers have developed a new series of oxadiazole-benzimidazole congeners as GSK-3β inhibitors. Compound **41** was found to possess high selectivity and potent *in-vitro* GSK-3β inhibitory activity with IC_{50} 0.0023µM. Further, its binding mode was determined by obtaining the X-ray co-crystal structure with the binding protein GSK-3β. Compounds were evaluated for GSK-3β inhibition activity in a non-RI kinase assay using Kinase-Glo reagent (Promega, U.S.A.) [88]. Similarly, the same group synthesized a series of sulfinyl benzofuran-oxadiazole conjugates and evaluated their GSK-3β inhibitory potential [89]. Compounds **42** and **43** with aliphatic side chain demonstrated good brain permeability and excellent activity with IC_{50} values 0.034 and 0.020 µM respectively. In addition these compounds showed good pharmacokinetic profiles.

On the other hand, Fukunaga and co-workers have synthesized a series of 2-(2-phenylmorpholin-4-yl)pyrimidin-4(3H)-ones and studied their GSK-3β inhibitory potential. Compounds **44**, **45** and **46** obtained from transformation of 2-oxoethylene moiety into morpholine moiety, were found to possess potent *in vitro* GSK-3β inhibitory activity demonstrating IC_{50} values of 0.012, 0.0065 and 0.00064 µM respectively. Out of these three, **44** were found to be orally active and inhibited *in vivo* tau phosphorylation in mice and showed moderate bioavailability in rats with high kinase selectivity. GSK-3β inhibition assay was performed using scintillation proximity assay (SPA) [90]. Similarly, Uehara and co-workers have developed a series of 6-(4-pyridyl) pyrimidin-4(3H)-ones and evaluated their activity against GSK-3β. In fact, this was an optimization study of a previous known hit

compound **47** which possesses sufficient chemical space to play around and exhibited IC_{50} value of 3 μM for GSK-3β inhibition. The optimization resulted in the synthesis of 2-substituted derivatives and compound **48**, a phenacyl derivative was found to be the most promising candidate from this series. It exhibited excellent GSK-3β inhibitory activity with IC_{50} value as low as 0.0089 μM. In addition, it showed good brain permeability and reduced tau phosphorylation in mouse brain [91].

(Figure 7)

Nitrogen containing heterocycles are well known for their diverse biological activities [92]. In view of this, several research groups have utilized them for the development of GSK-3 inhibitors (Figure 8). La Pietra and co-workers have synthesized a series of pyrazolopyrrolyl maleimide derivatives by a suitable structural modification of previously known GSK-3β inhibitor, **49**. The compounds were tested for their activity against GSK-3β and **50** was found to be the most active compound that inhibited GSK-3β with an IC_{50} 0.24 μM. It was also found to inhibit tau phosphorylation which was determined by cell based assay. Moreover, it was tested against 17 kinases and found to be a selective inhibitor of GSK-3 also exhibiting more than tenfold selectivity against CDK2. Physicochemical properties and Volsurf predictions showed that **50** could diffuse passively across the blood brain barrier. HEK-293 cell model was used to carry out the biological studies [93].

Similarly, Lu and co-workers have reported synthesis and neuroprotective as well as GSK-3 inhibitory properties of a series of quinoline derivatives. Several compounds were found to possess dual effects of inhibition of Aβ toxicity in MC65 cells and GSK-3β enzyme. Compounds **51** and **52** were found to exhibit neuroprotective activities in nanomolar to submicromolar concentrations both against amyloid β-induced MC65 cells and GSK-3β (IC_{50} 0.035 μM and 0.158 μM respectively for GSK-3β inhibition). Further, oral administration of compound **51** in a normal mouse model study indicated that **51** distributed both in brain and

pancreas in mice when administered in a dose of 5 mg/kg daily over 75 days. It showed no apparent toxicity determined by the examination of locomotor activity and liver transaminases and thus could be termed as safe for long-term study in AD mouse model [94]. In another work, based on the potent and highly selective GSK-3 inhibitor AR-A014418 (**53**) Monte and co-workers utilized the structural subunit of urea to synthesize a new series of GSK-3 inhibitors. Among this, benzothiazolyl urea derivative **54** showed an IC_{50} value of 0.140 µM and the pyridyl urea derivative **55** showed an IC_{50} of 0.098 µM, which indicated that both the compounds has shown two to threefold enhanced activity when compared to the reference compound **53** (IC_{50} value of 0.330 µM) [95]. Recently, Luo and co-workers reported a series of isonicotinamides as potent and selective GSK-3 inhibitors which were found to be oral active in a triple-transgenic mouse model of AD. Among these, **56** was found to the most potent as well as highly selective (GSK-3β/α IC_{50} = 0.0059/0.002 µM). Also, it significantly lowered phosphorylated tau levels in the AD model (pTau IC_{50} = 0.200 µM) [96].

3.2. GSK-3 inhibitors as anticancer agents

Cancer is caused due to uncontrolled proliferation of cells and can affect individuals of any age and is the reason of increased mortality around the world. It can invade and spread to other tissues in the body, often termed as metastasis. Cancers can be treated by chemotherapy, radiotherapy and in some cases surgically, however these methods sometimes cause unwanted effects on the patient, both physically as well as mentally. GSK-3 plays a key role in Hedgehog, NF-κB, β-catenin, Notch pathway and is negatively regulated by several pathways like Wnt, phosphatidylinositol 3' kinase(P13'K) pathway which makes it a potential target in developing GSK-3 inhibitors [9, 97]. Surprisingly, GSK-3 can play a dual role of both tumour suppressor as well as tumour promoter [10, 97]. GSK-3 is implicated in various cancers like oral [98], pancreatic [99], oesophageal

[100], ovarian cancer [101, 102] and many other. Many compounds with GSK-3 inhibitory potential are being developed as novel anti-cancer agents and have shown promising results [103, 104].

Brazilein (**57**), isolated from *Caesalpinia* sappan Linn from many years has been used as a traditional medicine in China and was reported to show immunosuppressant activity [105]. Tao and co-workers investigated the anti-cancer activity of Brazilein. Brazilein shows its activity by cell cycle arrest in G1 phase. Cyclin D1 is essential for progression from G1 to S phase and is decreased by Brazilein. Western blotting and RNA interference assay indicated that brazilein treatment activates GSK-3β and reduces β-Catenin levels which lead to cell arrest. Downregulation of GSK-3β/β-Catenin pathway can be considered as a mechanism by which it acts [106]. An advantage of brazilien is that it escapes the excretion by ABCB1 transporter to overcome ABCB1-mediated multidrug resistance in human tumour cells [107]. IC_{50} value against human breast cancer MCF-7 cells was found to be 7.23 ± 0.24 μmol/L [106].

Jeong and co-workers synthesized a series of isoxazol-indolin-2-one as potential anticancer agents. GSK-3 inhibitory activity of these compounds was tested against two tumour cell lines (DU145 and HT29). Most of the synthesized compounds were found to be potent with above 80% inhibitory activity at 100 μM. Amongst them, compound **58** was found to be the most active with 78% inhibition of tumour cell line HT29 at 20 μM and 72% inhibition of GSK-3β at 20μM [108].

Miambo and co-workers synthesised a series of isothiazolo[4,5-b]carbazole derivatives using a Diels Alder approach involving thermally induced indole-2,3-quinodimethane intermediates. Free NH group containing compounds **59, 60,** and **61** were found to display selective human carbonic anhydrase I inhibitory activities. The tetracyclic analogues bearing free NH group on the isothiazolinone ring system were also tested on other cancer

targets like DNA-binding, DNA topoisomerase I and kinases. Amongst these analogues, compound **61** was identified as an efficient GSK-3β kinase inhibitor displaying significant GSK-3β inhibitory activity with an IC_{50} of 2.8 μM [109].

Gaisina and co-workers synthesised a novel series of benzofuran-3-yl-(indol-3-yl) maleimides, as potent GSK-3β inhibitors. Amongst these, some compounds showed picomolar inhibitory activity towards GSK-3β and high selectivity against cyclin-dependent kinase 2 (CDK-2). Some of the GSK-3β inhibitors were tested in the pancreatic cancer cell lines MiaPaCa-2, HupT3, and BXPC-3. Compounds **62**, **63**, **64**, **65**, and **66**, (Table 2) were found to exhibit antiproliferative activity against most of the pancreatic cancer cells at low concentrations. Pancreatic cancer cells on treatment with GSK-3β inhibitors **63** and **66** resulted in suppression of GSK-β activity and also decreased the X-linked inhibitor of apoptosis (XIAP) expression, leading to significant apoptosis [110].

Zhao and co-workers synthesized a series of N-alkyl or aryl substituted isoindigo derivatives. The anti-proliferative activity of all target compounds against leukaemia cell lines (K562, L1210) was tested along with several human solid tumour cell lines (HCT-116, MGC80-3, A549, and HeLa). The most potent compound was found to be **67** as it could arrest cell cycle at S phase in K562 cells by down-regulating the expression of CDK2 and cyclin A and expression of Wnt/β-catenin signalling pathway proteins p-GSK-3β (Ser9), β-catenin and c-myc. Moreover, it could up-regulate the expression of GSK-3β, which plays a critical role in apoptosis and IC_{50} value of **67** was found to be 7.8 ± 0.5 μM against K562 cells [111].

3.3. GSK-3 inhibitors as anti-malarial agents

Malaria is a deadly disease caused by parasites that are transmitted to people through the bites of infected female *Anopheles* mosquito. It is caused by *Plasmodium* parasites namely

P. falciparum, *P. ovale*, *P. vivax* and many more. *Pf*GSK-3, the *P. falciparum* gene homologue of GSK-3β is an essential enzyme for the completion of asexual erythrocytic cycle of malaria parasite. *Pf*GSK-3 encodes a 452-amino-acid, 53-kDa protein with an *N*-terminal extension and also a well-conserved catalytic domain. Expression and intracellular localisation of *Pf*GSK-3 occurs during erythrocytic stages of malarial life cycle. *Pf*GSK-3 once synthesized, is rapidly transported to the erythrocyte cytoplasm where it associates with vesicle-like structures [112]. With the increase in the cases of *Plasmodium falciparum* resistance worldwide, *Pf*GSK-3β could be served as a promising target for identification of potent and selective anti-malarial drugs. In view of this, Fugel and co-workers developed a novel class of 3,6-diamino-4-(2-halophenyl)-2-benzoylthieno[2, 3-*b*]pyridine-5-carbonitriles as selective inhibitors of *Pf*GSK-3. In this process initial hits were identified using HTS. Further, compounds **68-72** were found to exhibit inhibitory activity towards *Pf*GSK-3 at submicromolar concentrations with high selectivity (Table 3) [113].

In another work, Coulibaly and co-workers synthesized an expanded series of *N*,*N*′-bis-(5-arylidene-4-oxo-3,5-dihydro-4H-imidazol-2-yl)diamines as anti-malarial agents. The synthesis was carried out by linking 2-amino-5-arylidene-imidazoline-4-one with various symmetric diamino linkers and compound **73** showed GSK-3α/β inhibition at micromolar concentrations with an IC_{50} 2.7 µM [114].

3.4. GSK-3 inhibitors as anti-diabetic agents

Diabetes is a chronic disease, which occurs due insufficiency in the production of insulin by the pancreas, or when the body is incapable of using the insulin which eventually leads to a condition called as hyperglycaemia. Symptoms are usually referred to as 3Ps which are polydipsia, polyuria and polyphagia. There are two main forms of diabetes: type 1 diabetes known as insulin-dependent or childhood-onset and type 2 diabetes known as non-insulin-

dependent or adult-onset diabetes. GSK-3β is considered to be an essential component in insulin-signalling pathway which regulates glucose homeostasis by negative regulating insulin-mediated glycogen synthesis [115]. GSK-3 plays a pivotal role in the development of insulin resistance and type 2 diabetes.[12, 115] Eldar-Finkelman and co-workers showed experimentally using C57BL/6J mice, how GSK-3 is linked to insulin resistance and development of type 2 diabetes [116]. Data obtained from the reported crystal structures has led to the identification of various potent and selective inhibitors which have been tested both *in vitro* and *in vivo* [117, 118].

In this regard, Seto and co-workers synthesised a series of 6,6,7-tricyclic quinolones containing the strained spirocycle moiety targeting GSK-3β. Amongst these, **74** having a cyclobutane ring on a spirocycle, showed GSK-3β inhibitory activity in both cell-free as well as cell-based assays with IC_{50} as well as EC_{50} values 0.036 µM and 3.2 µM respectively. Interestingly, **74** also decreased the plasma glucose concentration dose-dependently after an oral glucose tolerance test in mice [119].

In another work, Engler and co-workers synthesized a series of 3-Imidazo[1,2-a]pyridin-3-yl-4-(1,2,3,4-tetrahydro-[1,4]diazepino-[6,7,1-hi]indol-7-yl)pyrrole-2,5-diones which were found to be potent inhibitors of GSK-3 with high selectivity when tested on Zucker fatty rat model which is a well-established animal model in case of type 2 diabetes [120]. Compounds **75-80** (Table 4) showed oral activity in an *in-vivo* model of type II diabetes which were Zucker diabetic fatty (ZDF) rats and compounds **77** and **80** were found to have desirable PK properties with oral bioavailability of 45 ± 4 and 23 ± 4 % respectively [121].

(Figure 9)

3.5. GSK-3 inhibitors in other disorders

3.5.1. Cerebral Ischemic Disease

Cerebral ischemia or brain ischemia, is a condition which occurs due to insufficient blood supply to the brain which is below the metabolic demand. This leads to cerebral hypoxia and irreversible damage to brain tissue causing cerebral infarction or ischemic stroke. It is one of the sub-types of stroke in addition to subarachnoid haemorrhage and intracerebral haemorrhage. Cerebral ischemia is characterized by excess glutamate release, insufficient nutrient supply, low oxygen and glucose supply in the brain.

GSK-3β inhibition is found to have neuro-protective effects in patients suffering from cerebral ischemia and helps improves neuronal survival [122]. Ye and co-workers synthesized a novel series of 3-([1,2,4]triazolo[4,3-a]pyridin-3-yl)-4-(indol-3-yl)-maleimides, using bioisostere and ring substitution principle, to obtain potent and specific inhibitors of GSK-3β which could be used for the treatment of cerebral ischemia. Cellular neuro-protective assay was performed and compounds **81**-**85** displayed potent neuro-protective effects in different neuronal injury models associated with cerebral ischemia (Table 5) [123].

3.5.2. Human African Trypanosomiasis (Sleeping Sickness)

Human African trypanosomiasis (HAT), also known as sleeping sickness, is caused by a parasite transmitted by the bite of 'Glossina' insect, commonly known as the *tsetse* fly. *Trypanosoma brucei* which is a vector-borne parasite is responsible for causing the infection. Following the bite, the parasite multiplication takes place in the lymph and the blood, causing headache, fever, weakness, pain in the joints and stiffness. The infection is mostly asymptomatic in initial period and during later stages, the parasite can cross the blood-brain barrier and can migrate to the central nervous system where it causes various neurological changes which lead to psychiatric disorders, seizures, coma and ultimately death.

Protein kinases in *T. Brucei* are considered to be the potential drug targets for the treatment of HAT. The parasite genome contains two kinases i.e., TbGSK-3 short and TbGSK-3 long which are highly homologous to human GSK-3 enzyme, making it a potential target for treatment of this disease [124]. In a recent work, Urich and co-workers synthesised a series of aminopyrazole inhibitors which binds to TbGSK-3 short. The inhibitors were also tested against the closely related off-targets HsGSK3β and HsCDK2. The most potent compound **86** has micro-molar affinity for TbGSK3 short and is selective over HsCDK2 and HsGSK3β, and exhibited good kinase profile. IC_{50} values of **86** towards TbGSK-3, HsGSK-3 was found to be 0.0001 µM and 0.330 µM respectively [125]

3.5.3. Osteoporosis

Osteoporosis or "porous bone" is a condition which mainly affects the bones leading to its weakening. Normally, some of the parts of a healthy bone look like a honeycomb when observed under a microscope but in case of osteoporosis, the holes and spaces in the honeycomb appear indicating loss of bone density or mass rendering it abnormal. Interestingly, GSK-3 has been observed to play a role in remodelling of bones [126].

Combined genetic and genomic studies led to a conclusion that a Wnt interacting protein (Frzb1) is key element influencing peak bone density in humans as well as in mice [127, 128]. Gong and co-workers synthesized a series of maleimide derivatives which were found to be highly potent with good selectivity for GSK-3β. The most potent compound **87** showed remarkable activity with an IC_{50} of 0.0006 µM and over 100-fold selectivity against a panel of other kinases. In addition, it showed very good efficacy in rat osteoporosis models [129].

(Figure 10)

Conclusion

GSK-3 has emerged as a potential target due to its central role in major cellular and signalling pathways and has occupied a prime position in the study of progression of various chronic disorders affecting the mankind. Initially considered as a target for developing antidiabetic drugs, its spectrum has grown to a wider range of diseases and treatment on which it can have a striking influence. Discovery of lithium as a direct inhibitor of GSK-3 was a major breakthrough in this area. Many natural products have also contributed in providing leads for the drug discovery in the realm of GSK-3 inhibitors. With the emergence of non-ATP competitive and allosteric inhibition mechanisms for GSK-3 inhibition, a new area has opened up which may have far reaching advantages in tackling side effects as well as toxicity. In addition, computational screening methods have also aided the drug discovery process giving an insight into ligand affinity and receptor binding properties. The present review summarizes the efforts that have been made to find new GSK-3 inhibitors and their application to treat various human disorders. In this regard, there are quite a few molecules targeting GSK-3 under clinical investigations. Though, the entry of some of the GSK-3 inhibitors in the clinical and pre-clinical phases has been encouraging, the dream of having a potent GSK-3 inhibitor in the market is still unrealized. Also, the burdens of drug resistance and side-effects have challenged the scientists globally, yet the uniqueness of this enzyme outweighs all the hurdles and is anticipated to keep inspiring the future scientists to achieve a major breakthrough in this area in the near future.

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Table Legends:

Table 1: Benzofuran-3-yl-(indol-3-yl)maleimides as GSK-3 inhibitors.

Table 2: 3,6-diamino-4-(2-halophenyl)-2-benzoylthieno[2, 3-*b*]pyridine-5-carbonitriles GSK-3 inhibitors.

Table 3: 3-Imidazo[1,2-a]pyridin-3-yl-4-(1,2,3,4-tetrahydro-[1,4]diazepino-[6,7,1-hi]indol-7-yl)pyrrole-2,5-diones as GSK-3 inhibitors.

Table 4: 3-([1,2,4]triazolo[4,3-a]pyridin-3-yl)-4-(indol-3-yl)-maleimides as GSK-3 inhibitors.

Table 1:

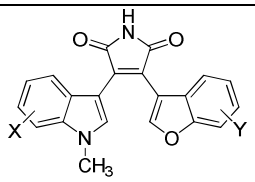
General Structure	 **62-66**		
Compound	**X**	**Y**	**IC_{50}(µM)**
62	5-F, 6-I	7-OCH_3	0.247
63	5-F, 6-Cl	H	0.184
64	5-F, 6-Cl	7-OCH_3	0.260
65	5,7-dibromo	7-OCH_3	0.0887
66	5,6-methylenedioxy	5-F	0.710

Table 2

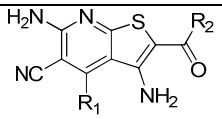
General Structure	 **68-72**		
Compound	**R_1**	**R_2**	**IC_{50}(µM)**
68	2-MeOPh	Ph	6
69	2-IPh	3-ClPh	0.91
70	2-BrPhe	3-ClPh	0.6
71	2-ClPhe	3-ClPh	0.48
72	2-ClPhe	3-CNPh	0.5

Table 3

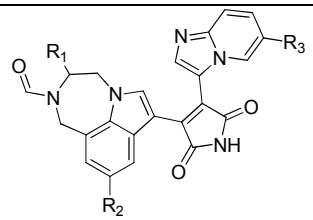
General Structure	 **75-80**			
Compound	**R_1**	**R_2**	**R_3**	**IC_{50} (μM)**
75	OiPr	H	H	0.0013
76	Piperidinyl	H	H	0.002
77	Piperidinyl	H	Me	0.0052
78	Morpholinyl	H	H	0.0013
79	Dimethylaminyl	H	H	0.0016
80	Piperidinyl	F	H	0.0011

Table 4

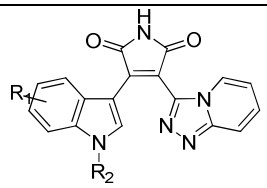
General Structure	 **81-85**		
Compound	**R_1**	**R_2**	**IC_{50} (μM)**
81	7-Me	Me	0.1054
82	5-Cl	Me	0.0741
83	5-Br	Me	0.0635
84	H	Butyl	0.0697
85	H	Isopropyl	0.013

Figure Legends

Figure 1*:* GSK-3 inhibitors currently under clinical investigations.

Figure 2*:* Maleimide containing small molecule inhibitors of GSK-3.

Figure 3: Pyridine derivatives and pyrimidine containing small molecule inhibitors of GSK-3.

Figure 4: Miscellaneous compounds.

Figure 5: Oxadiazole containing small molecule inhibitors of GSK-3 in the treatment of Alzheimer's disease.

Figure 6: Pyrimidinone containing small molecule inhibitors of GSK-3 in the treatment of Alzheimer's disease.

Figure 7: GSK-3 inhibitors based on N-containing heterocycles in the treatment of Alzheimer's disease.

Figure 8: GSK-3 inhibitors as anticancer, antimalarial and antidiabetic agents.

Figure 9: Small molecule inhibitors of GSK-3 which are therapeutically active against diseases like cerebral ischemia, Human African Trypanosomiasis (HAT) and osteoporosis.

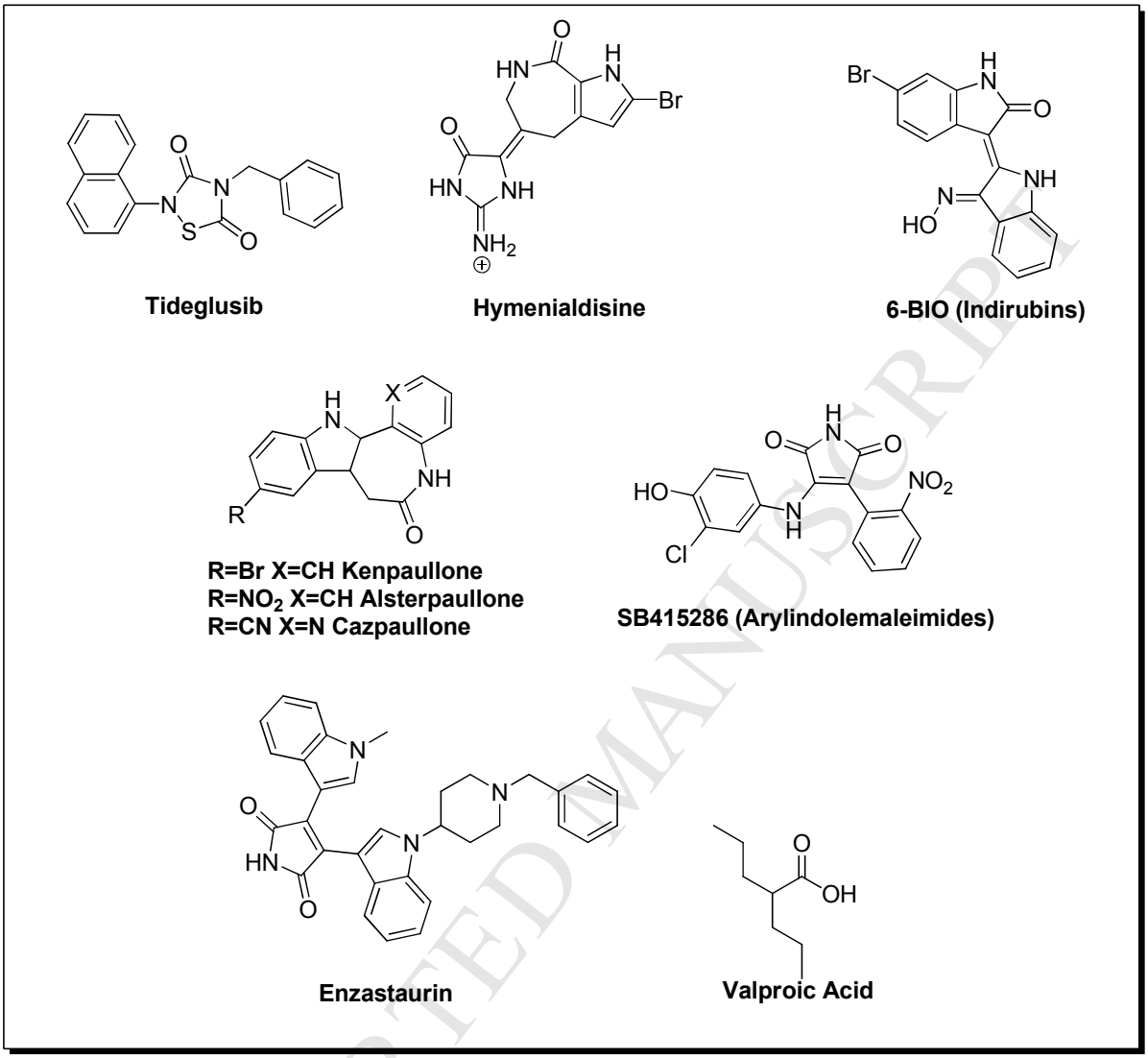


Figure 1

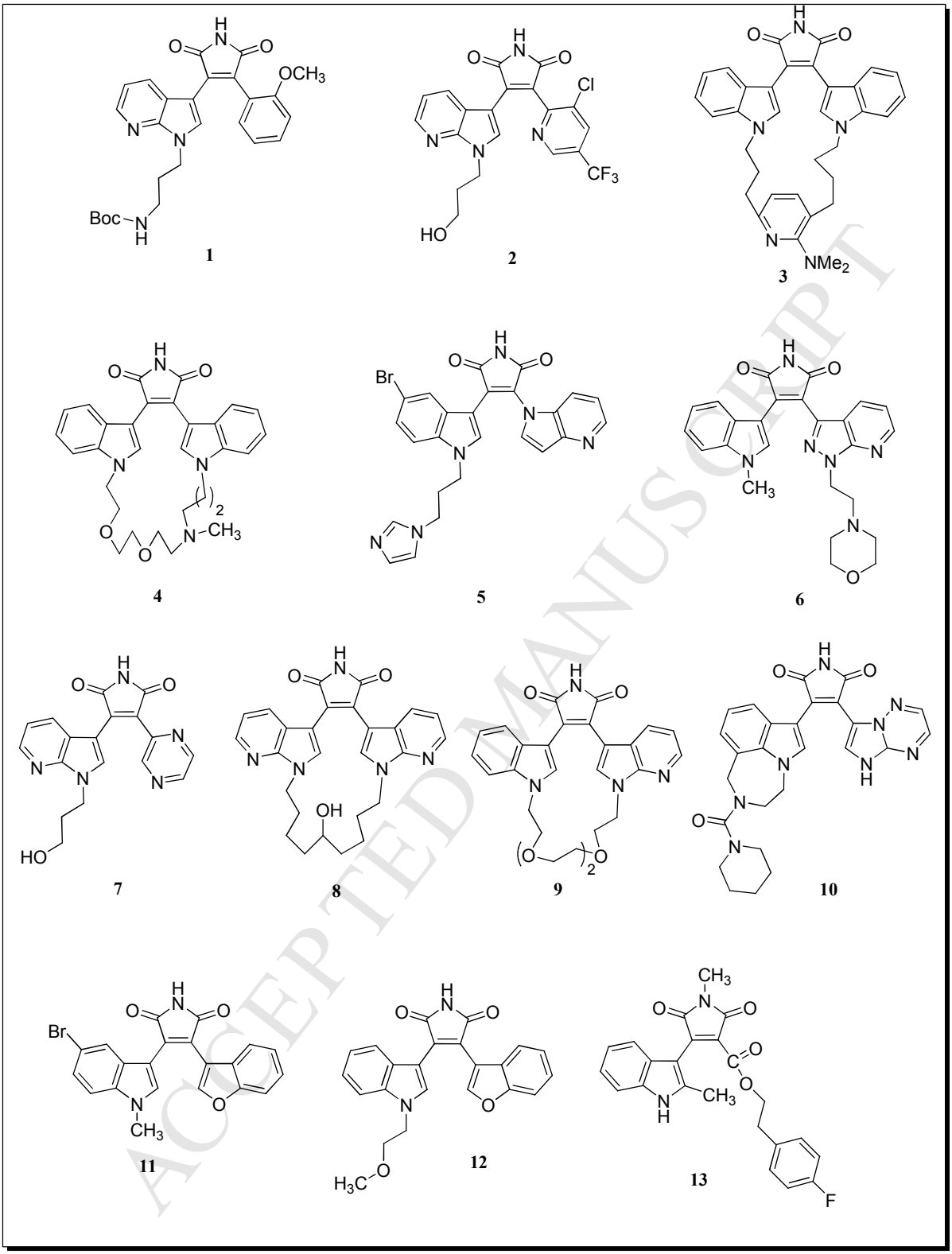


Figure 2

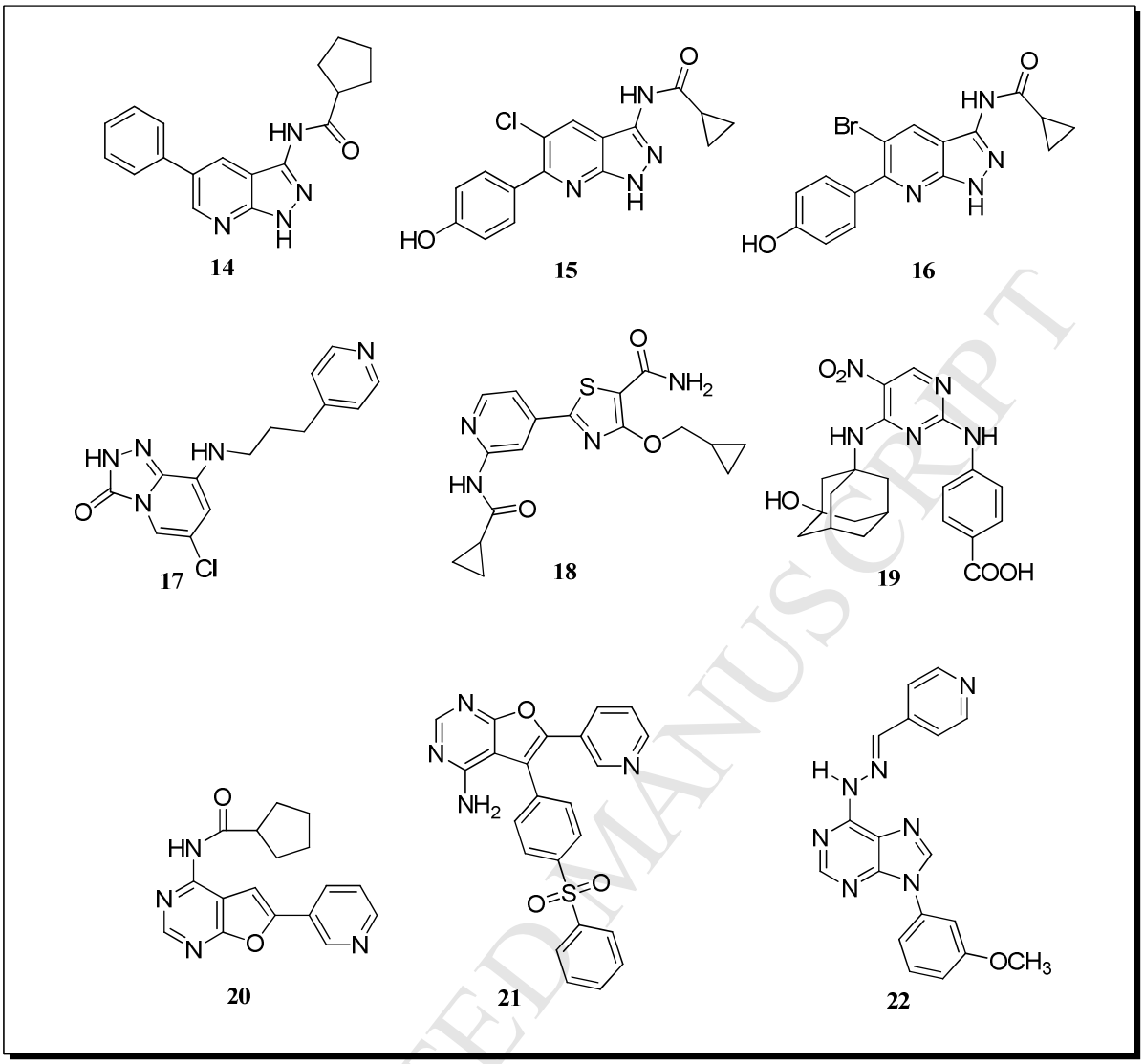


Figure 3

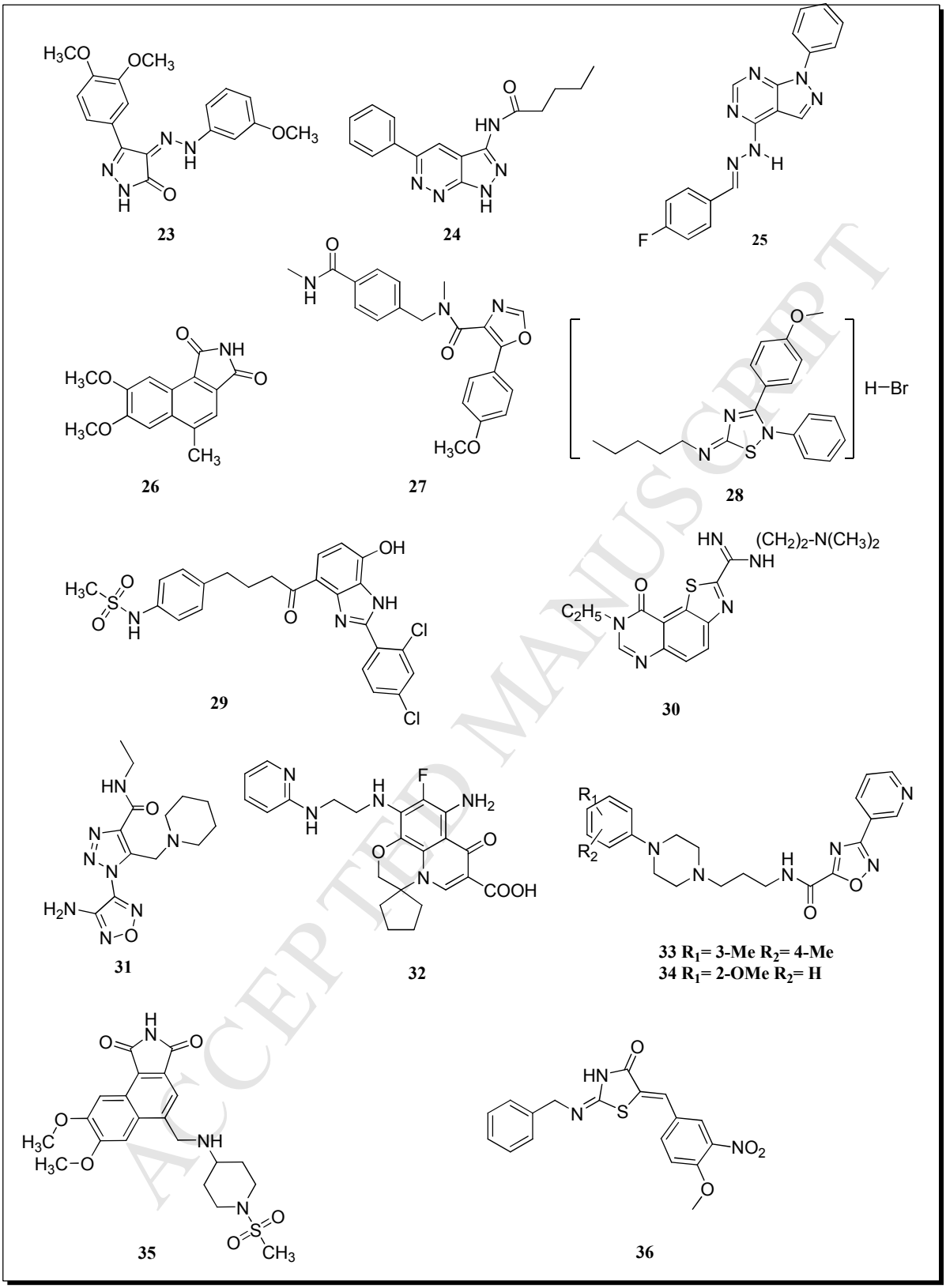


Figure 4

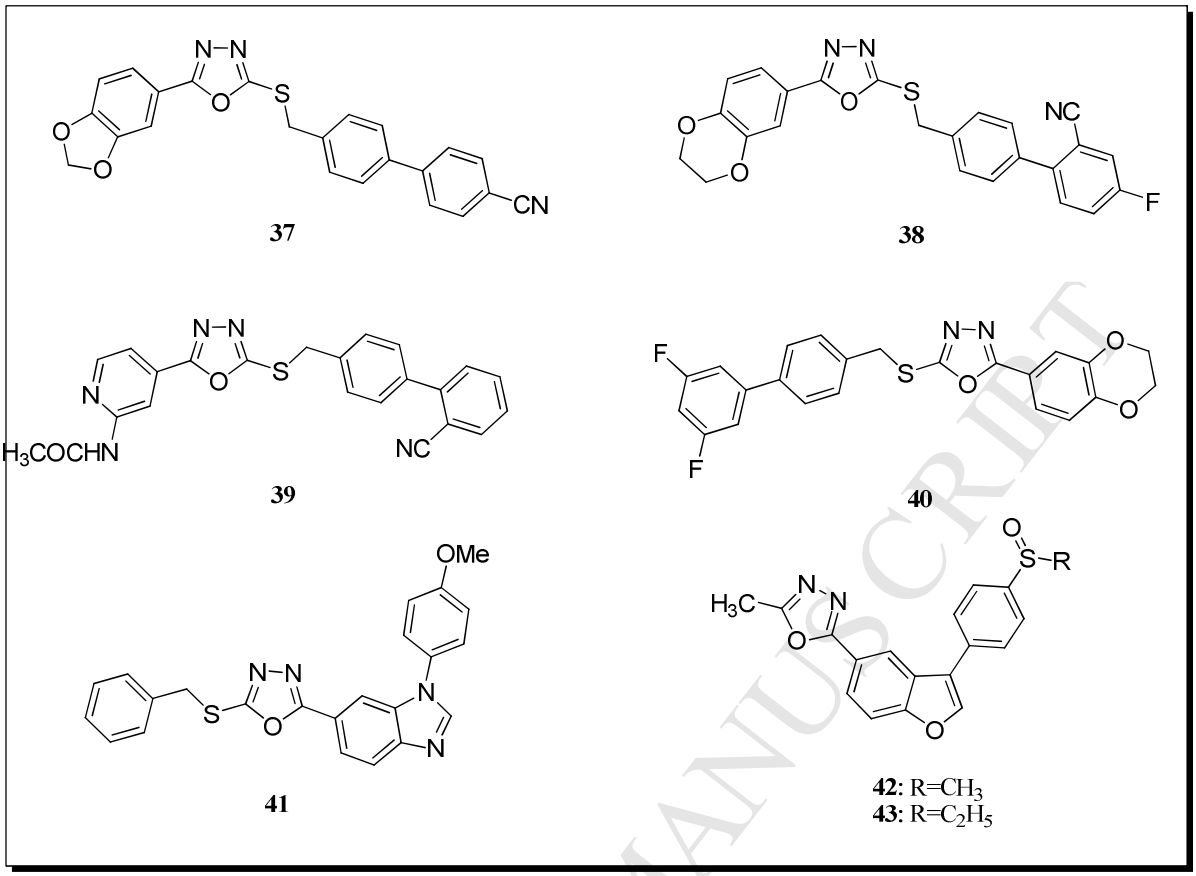
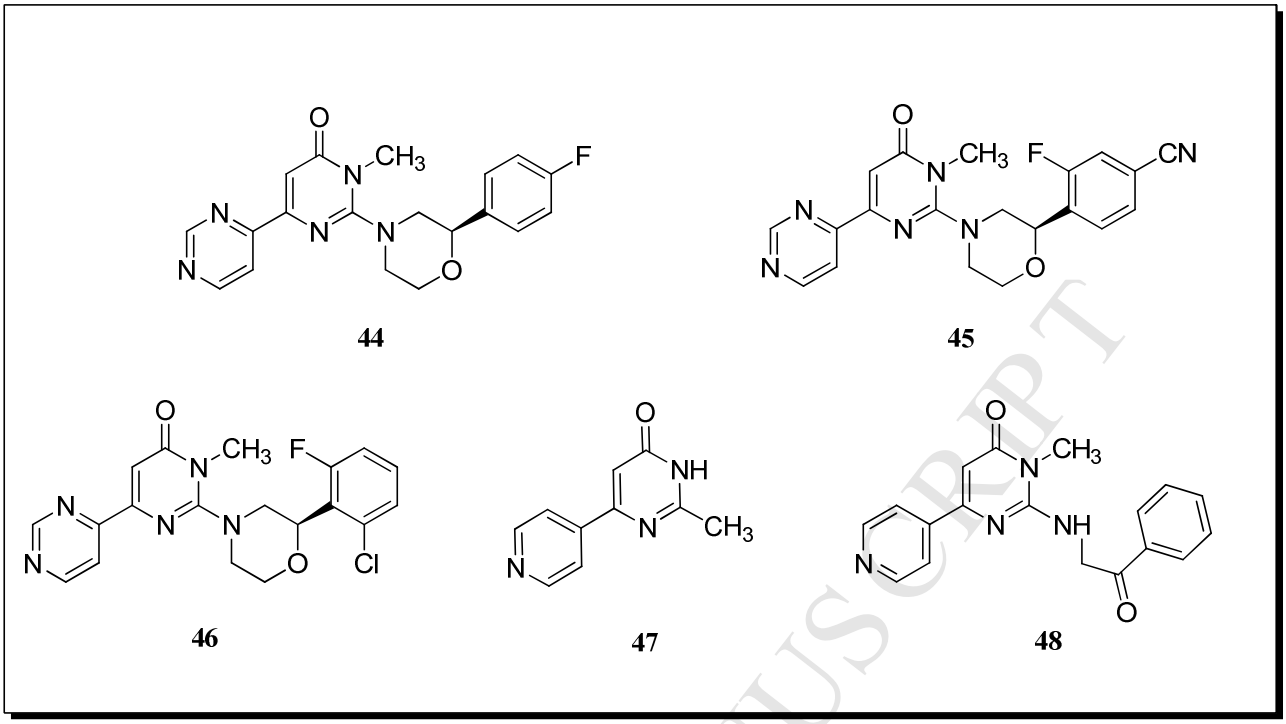


Figure 5



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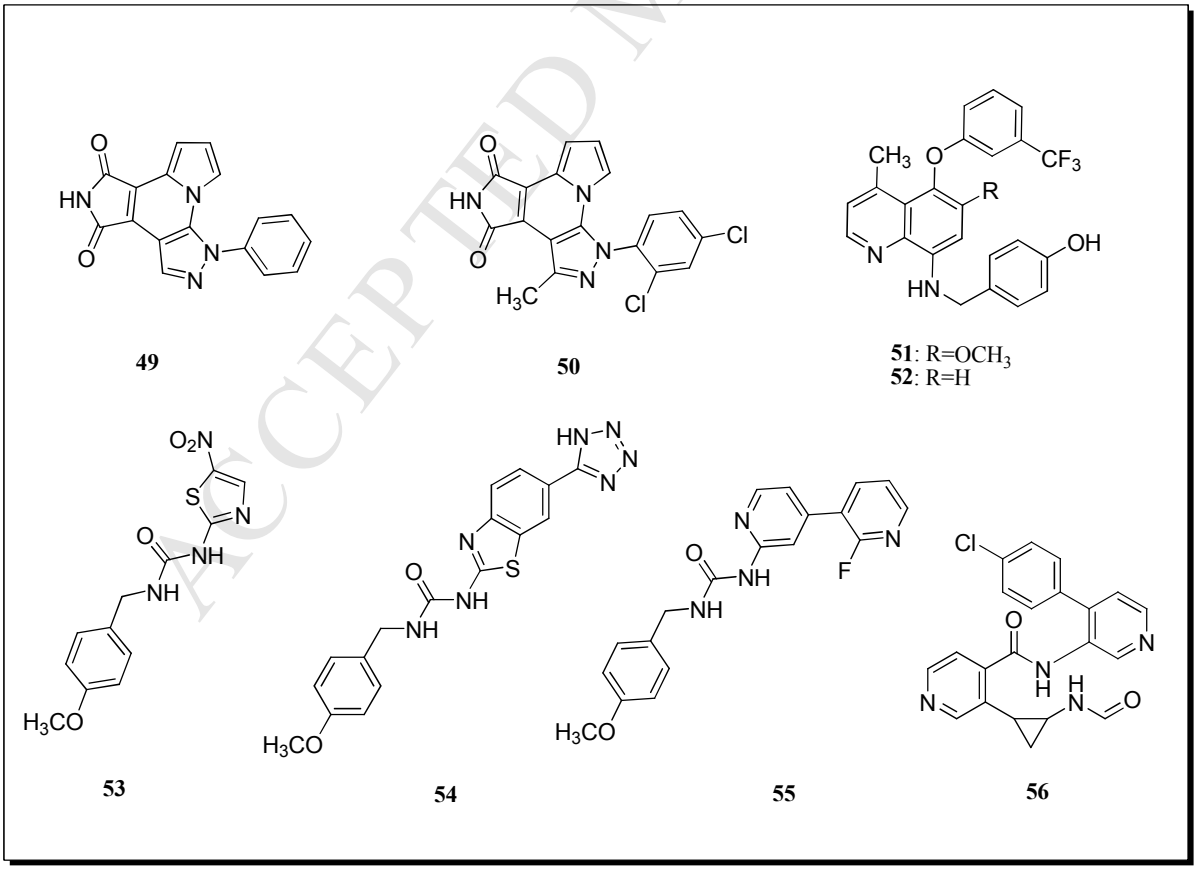

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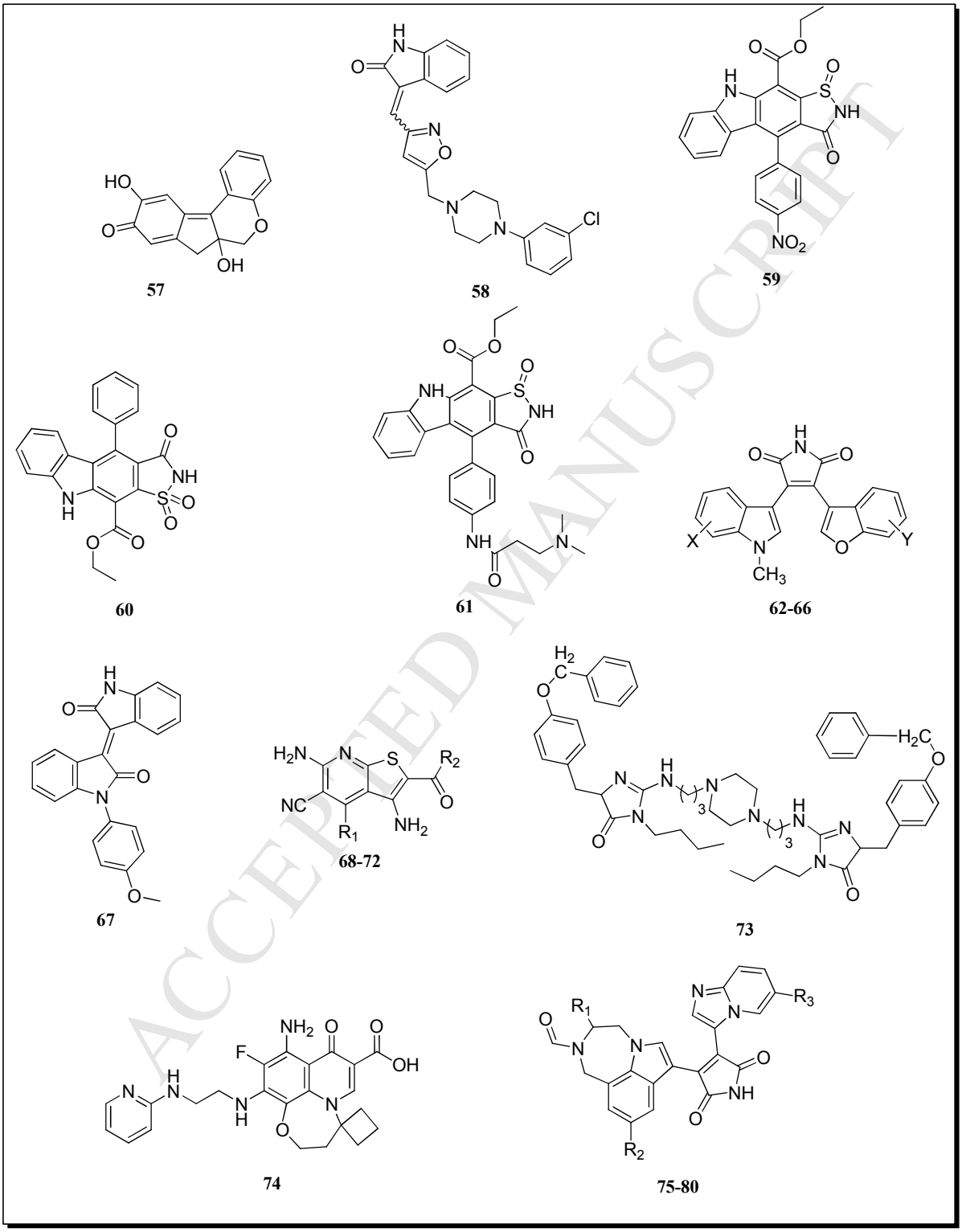

Figure 8

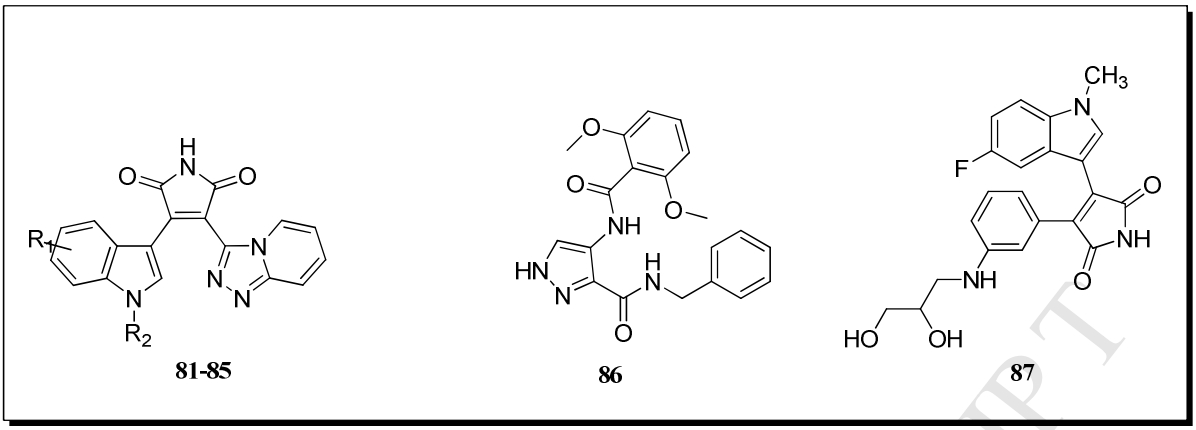

Figure 9

Highlights

- GSK-3 is a multifunctional serine/threonine protein kinase.
- Targeting GSK-3 using inhibitors has been a successful strategy.
- GSK-3 inhibitors have multifarious applications in various disease conditions.
- Many GSK-3 inhibitors have shown promiscuous results under clinical trials.
- In the present review, recent developments in GSK-3 inhibitors have been discussed.