Aromatic Heterocycle-Based DPP-IV Inhibitors: Xanthines and Related Structural Types

Bruce G. Szczepankiewicz* and Ravi Kurukulasuriya

Metabolic Disease Research and Target & Lead Discovery, Abbott Laboratories, Abbott Park, IL, 60064, USA

Abstract: Xanthines and xanthine-like DPP-IV inhibitors were first disclosed in 2002. Since then, several dozen accounts of xanthine-based DPP-IV inhibitors have been published. Only a few presentations and journal articles have appeared, with the vast majority of information coming from the patent literature. DPP-IV inhibitors related to the xanthines include purine analogues with other arrangements of the nitrogen atoms in the core structure, imidazoles, uracils, pyrimidines, pyridines, and some fused pyridines. At least one compound derived from the xanthines has advanced into clinical trials, making it likely that these molecules will play a major role in the DPP-IV inhibition arena over the next several years.

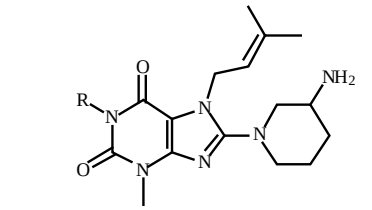
INTRODUCTION

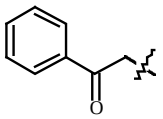
The history and significant milestones of dipeptidyl peptidase-IV (DPP-IV) and DPP-IV inhibition are subjects of the article by Hans Demuth in this special issue of *Current Topics in Medicinal Chemistry* [1]. Aromatic heterocycle-based DPP-IV inhibitors have become an important class in this arena over the past five years. This article will cover three classes of DPP-IV inhibitors: 1. xanthines and xanthine mimetics, 2. pyridines and pyrimidines, and 3. imidazoles and uracils. Each of these sub-classes bears some resemblance to the others, as the core serves to orient peripheral groups that maintain several points of contact necessary for potent DPP-IV inhibition. Heterocycles that were not derived from xanthine-based inhibitors, and heterocycles that do not exhibit overlapping structure-activity relationships with xanthines will not be covered in this review.

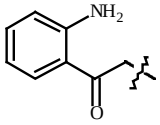
1. XANTHINES AND XANTHINE-BASED HETEROCYCLES

The biological activity of xanthine-based alkaloids has been known for nearly two hundred years, dating back to the isolation of caffeine in 1820 by Runge. Due to the wide array of biological activities seen with purines, and the role that purine alkaloids including xanthines have played in the history of organic chemistry, natural xanthine alkaloids and synthetic xanthine analogues are present in the screening collections of most pharmaceutical companies [2]. These archival compounds were the original sources of the xanthine-based DPP-IV inhibitors.

The first patents describing the DPP-IV-inhibitory activity of xanthines came from Novo-Nordisk [3-9] and Boehringer-Ingelheim [10]. The Novo-Nordisk group described the straightforward synthesis of inhibitors such as xanthine **1** starting from 8-chlorotheophylline (**2**). (Scheme **1**) This route allows for easy modification of the N-7 and C-8 positions, and many examples of such analogues appear in both the Novo-Nordisk and the Boehringer-Ingelheim patents. As xanthines lacking N-1 and N-3 substituents are also available, substitution at these positions is possible as well. The Boehringer-Ingelheim group disclosed some IC_{50} data with their xanthines, indicating that the IC_{50} values vs. DPP-IV for compounds **3**-**5** were in the 1-5 nM range. (Fig. (**1**)) The Novo-Nordisk group disclosed no biological activity data in their patents, but a later presentation included more information [11] (Fig. (**2**)). Xanthine **6** was a very potent DPP-IV inhibitor with IC_{50} = 4 nM. It was highly selective against other dipeptidyl peptidases including DPP-II, DPP-8, and DPP-9. Selectivity against other dipeptidyl peptidases is a desirable property for DPP-IV inhibitors,



3 R =  IC_{50} = 5 nM

4 R =  IC_{50} = 3 nM

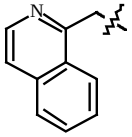
5 R =  IC_{50} = 2 nM

Fig. (1). Some selected DPP-IV inhibitors from Boehringer-Ingelheim.

*Address correspondence to this author at Metabolic Disease Research, Abbott Laboratories, R4MC AP10/L12, 100 Abbott Park Road, Abbott Park, IL 60064-6098, USA; Tel: (847)935-1559; Fax: (847) 938-1674; Email: bruce.szczepankiewicz@abbott.com

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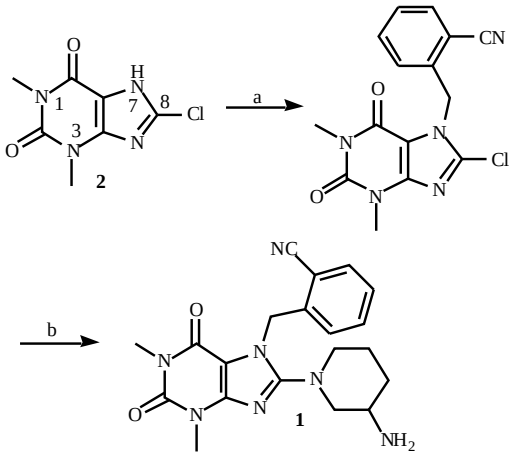

Reagents and Conditions: a) (2-cyano)benzyl bromide, K_2CO_3, KI, DMF, 25 ºC (93%); b) 3-aminopiperidine dihydrochloride, Et_3N, *i*-PrOH, 130 ºC (microwave), (43%).

Scheme 1. Novo-Nordisk synthesis of xanthine-based DPP-IV inhibitors.

since investigators at Merck have shown that activity against some of these can lead to toxicity [12]. *In vivo* inhibitory data were presented for a related analogue, fluorophenacyl xanthine **7,** though an IC_{50} value was not disclosed. At a dose of 10 mg/kg in normal Wistar rats, plasma DPP-IV activity remained below 5% of vehicle dosed animals for over 10 h. The calculated ED_{50} was 2mg/kg. Elaborating further on the SAR of the xanthines, the same group noted that the nitrogen atom proximal to the xanthine is crucial for potent DPP-IV inhibition (compounds **8** and **9**). The most potent compounds were all N-3 phenacyl substituted xanthines, with several examples (**10**-**14**) giving IC_{50} values below that of **6**.

The investigators at Boehringer-Ingelheim continued a vigorous effort to pursue xanthine-based DPP-IV inhibitors following their initial disclosure [13-25]. Another team at Eisai also published a series of patents on xanthine-based DPP-IV inhibitors [26-28]. Both of these groups included IC_{50} data in their patents, elucidating more of the SAR about the xanthine core. (Fig. (**3**), Fig. (**4**)) Many examples bear a 2-butynyl substituent at N-7, which can effectively replace a butenyl or benzyl group while maintaining excellent inhibitory potency vs. DPP-IV. The data indicate that C-8 piperazine or (3-amino)piperidine groups are approximately equipotent, (compounds **15**-**19**) consistent with the results presented by the Novo-Nordisk team [11]. The Boehringer-Ingelheim investigators also showed that an open chain amine maintained inhibitory potency (compounds **20**-**22**). There are hundreds of examples of N-1, C-2, and N-3 substitution in these patents, and it is clear from the IC_{50} data in Fig. (**1**-**3**) that very different substituents at N-1, C-2, and N-3 can give potent DPP-IV inhibitors. Additionally, both the Boehringer-Ingelheim and Eisai groups prepared 1*H*-imidazo[4,5-d]pyridazine (**23**, **24**) and 3*H*-imidazo[4,5-c]pyridine (**25**) cores for some active analogues [29-33] (Fig. (**5**)). The Boehringer-Ingelheim group [34] and another group at Fujisawa [35] also claimed compounds based on a hydrazide-type structure (**26**, **27**). Thus, major changes in the region from N-1 to N-3 (xanthine numbering) are tolerated.

A series of patents from Sumitomo claimed xanthines and xanthine analogues. The Sumitomo group also disclosed some pyrazolopyridine-based inhibitors. The arrangement of the heteroatoms in the core was important for DPP-IV activity, as exemplified by the difference in potency between pyrazolopyridines **28**-**30**. (Fig (**6**)) Other analogues (*eg.* **31**, **32**) resembled the xanthines and analogues shown in Fig. (**1**-**5**) [36-41].

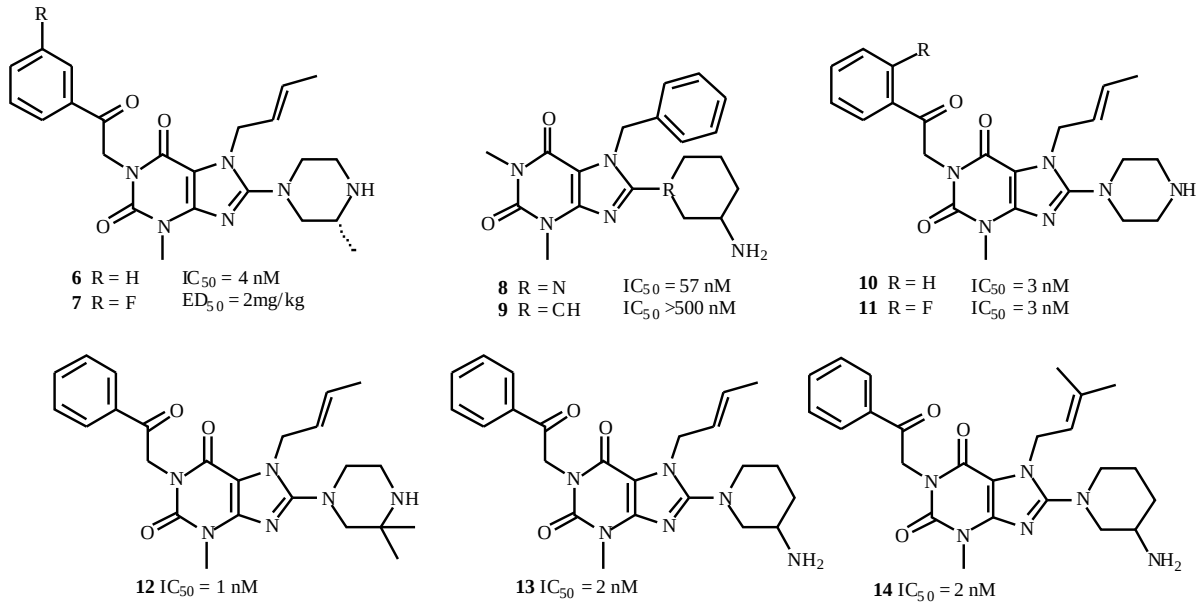

Fig. (2). Novo-Nordisk xanthine-based DPP-IV inhibitors with biological data.

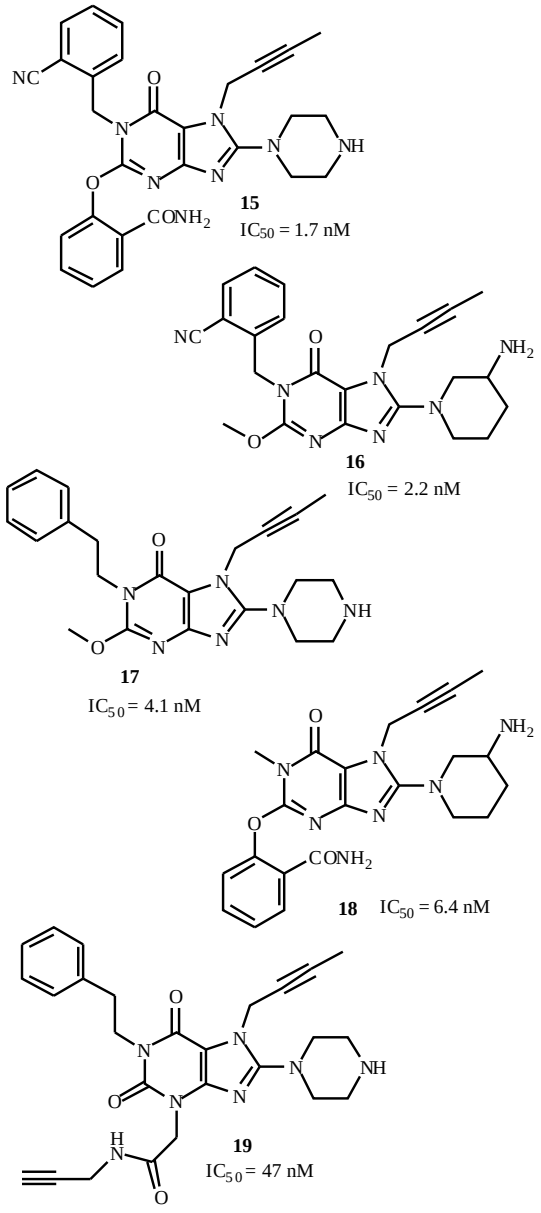

Fig. (3). Some Eisai xanthine-based DPP-IV inhibitors with IC_{50} data.

Some further SAR information about the C-8 position was disclosed by Ansorge and co-workers at the Institut für Medizintechnologie Magdeburg [42,43] (Fig (**7**)). Their data demonstrated that a tertiary amine distal to the C-8 attachment point (**33**, **34**) was much less active than a secondary amine (**35**, **36**). More information about this position was provided by investigators at Sanofi-Aventis who disclosed some IC_{50} data on diazabicyclic amines at xanthine C-8 (**37**, **38**) [44,45] (Fig (**8**)). The Sanofi-Aventis group also incorporated an 8-(aminoalkyl)ether (**39**)or an 8-(aminoalkyl) thioether (**40**-**42**) into the inhibitor scaffold. [46,47] (Fig. (**9**)). The potent DPP-IV inhibition demonstrated with these

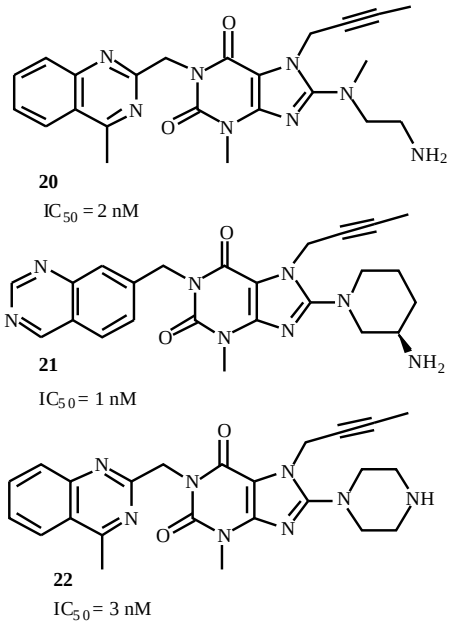

Fig. (4). Different C-8 amino groups and N-3 substituents maintain potency.

compounds indicates that the point of attachment to the xanthine C-8 need not be an amine. A tertiary center imparted greater activity than a methylene group adjacent to the sulfur atom.

A 2003 disclosure from Eisai showed a different arrangement of the amine and butynyl groups about the xanthine core [48] (Fig. (**10**)). These compounds were potent inhibitors, with purine-8-one **43** giving an IC_{50} value = 2.9 nM. Because they lack a C-2 carbonyl group, these are not true xanthines, but the purine nucleus remains intact.

Takeda/Syrrx also claimed some xanthine-like compounds as DPP-IV inhibitors [49,50] (Fig (**11**)). Most xanthine-based DPP-IV inhibitors bear an amino group and a benzyl, alkenyl, or alkynyl group both attached to the imidazole ring. However, the Takeda/Syrrx inhibitors are substituted on the pyrimidine ring (**44**). Since the groups that seem to be most critical for DPP-IV inhibition are no longer attached to the imidazole ring, these investigators modified the imidazole ring and claimed a variety of fused-heterocycles not seen in other DPP-IV inhibitor patents. (Fig. (**11**)) These heterocycles include benzopyrimidine (**45**), pyridopyrimidine (**46**), and triazolopyrimidine (**47**). No IC_{50} data were included in the patents disclosing these novel cores.

More distantly related to the xanthines are isoquinoline, quinoline, benzimidazole, and benzotriazole-based DPP-IV inhibitors from Takeda/Syrrx. (Fig. (**12**)) The isoquinolines were the first to appear in 2002 [51], followed by the quinolines [52,53], then the benzimidazoles and benzotriazoles. [54] Limited biological data were disclosed with these compounds, but isoquinoline **48** gave an IC_{50} = 280 nM, while quinoline **49** gave an IC_{50} = 710 nM. An aromatic core, an alkyl amine, and a substituted phenyl group are

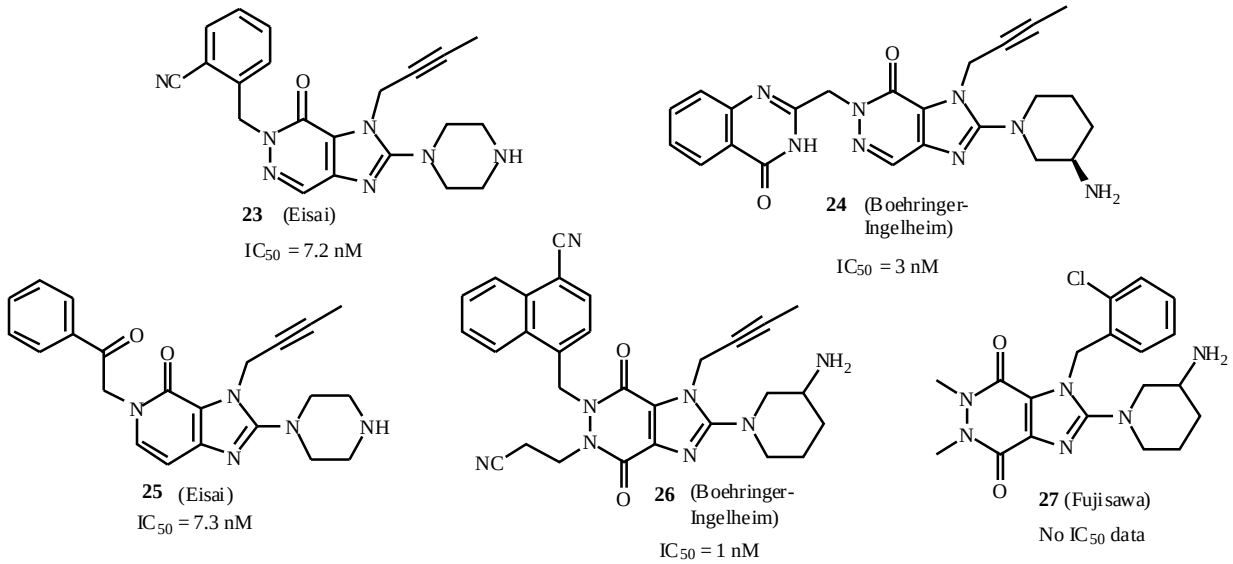

Fig. (5). Xanthine core modifications from Boehringer-Ingelheim Eisai, and Fujisawa.

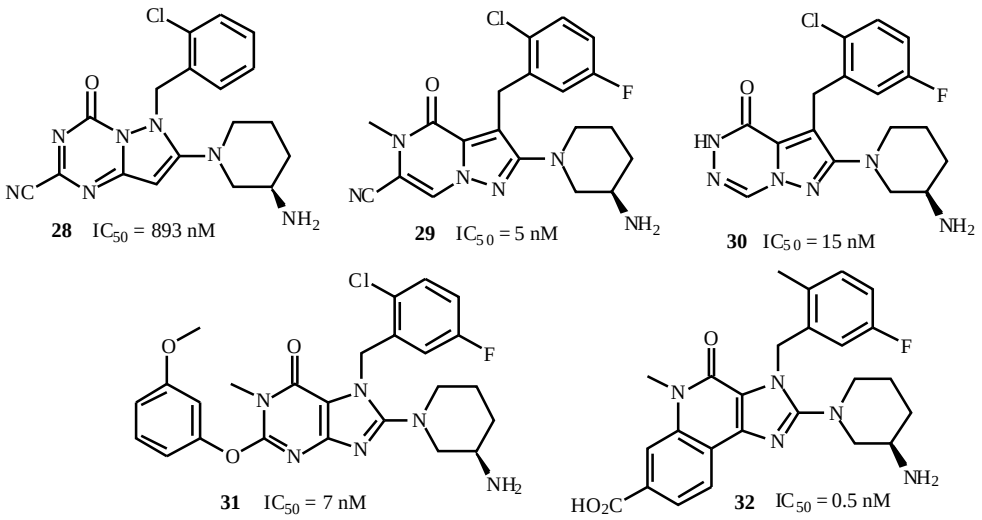

Fig. (6). Xanthine analogues from Sumitomo.

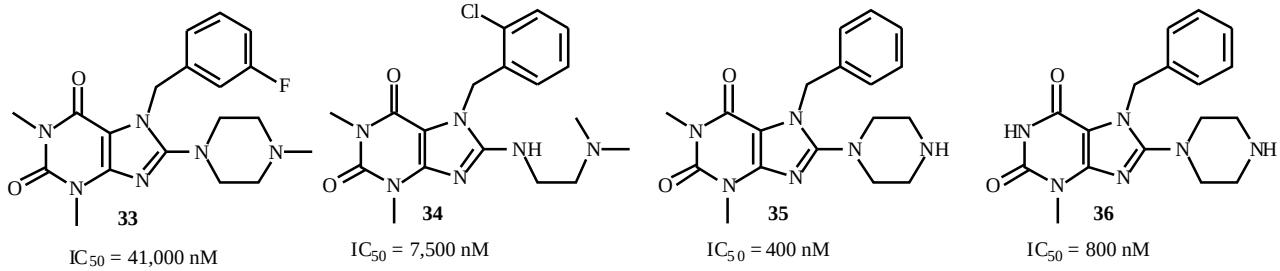

Fig. (7). C-8 tertiary amines are inferior DPP-IV inhibitors.

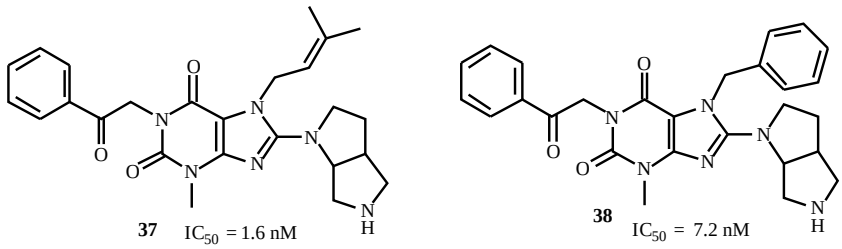

Fig. (8). Recent examples of bicyclic amines.

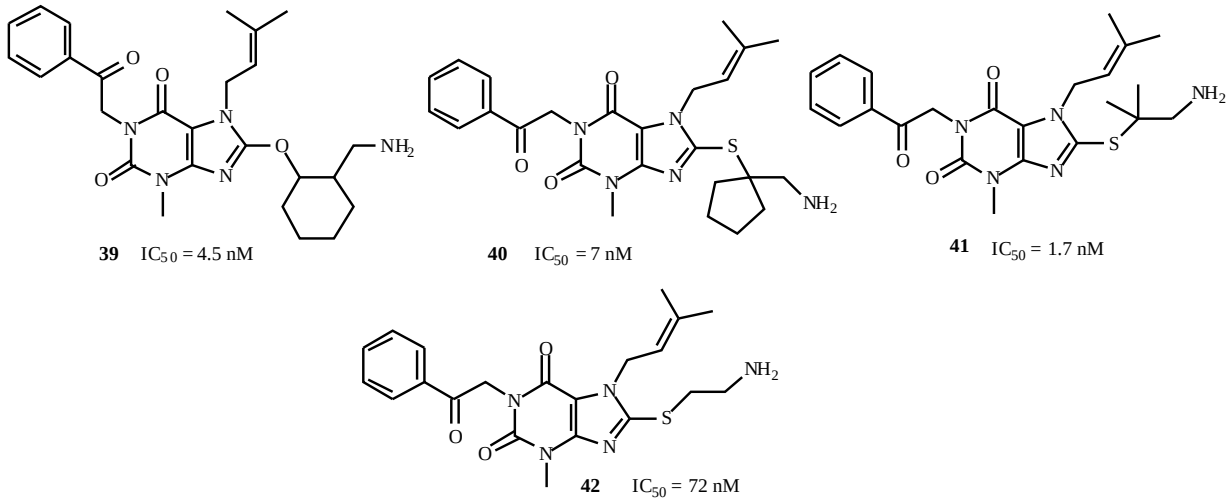

Fig. (9). Ether and thioether linkages at C-8.

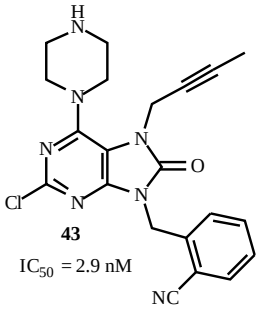

Fig. (10). An example of Eisai purine-8-one based DPP-IV inhibitors.

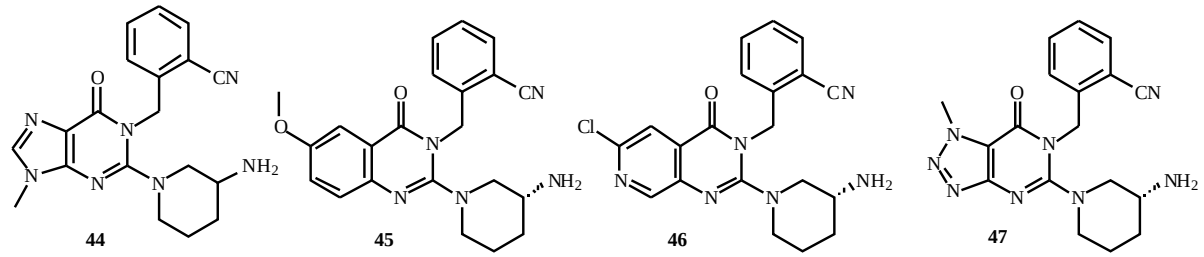

Fig. (11). Takeda/Syrrx compounds substituted on the pyrimidine ring.

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