

## Substituted 3-Imidazo[1,2-*a*]pyridin-3-yl-4-(1,2,3,4-tetrahydro-[1,4]diazepino[6,7,1-*h*]indol-7-yl)pyrrole-2,5-diones as Highly Selective and Potent Inhibitors of Glycogen Synthase Kinase-3

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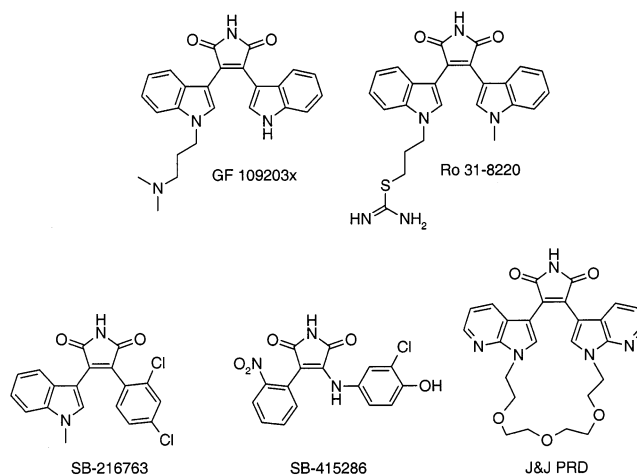
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**Abstract:** Glycogen synthase kinase-3 (GSK3) is involved in signaling from the insulin receptor. Inhibitors of GSK3 are expected to effect lowering of plasma glucose similar to insulin, making GSK3 an attractive target for the treatment of type 2 diabetes. Herein we report the discovery of a series of potent and selective GSK3 inhibitors. Compounds **7–12** show oral activity in an in vivo model of type II diabetes, and **9** and **12** have desirable PK properties.

Type 2, or noninsulin-dependent diabetes mellitus (NIDDM), afflicts 120 million people worldwide and is estimated to rise to over 200 million by the year 2010.<sup>1</sup> NIDDM accounts for approximately 90% of all cases of diabetes and is characterized by an inability of the body to effectively respond to insulin secreted by the pancreas, or insulin resistance.<sup>2</sup> GSK3 is a serine-threonine kinase encoded by two independent genes, GSK3- $\alpha$  and - $\beta$ .<sup>3</sup> Purified GSK3- $\alpha$  and - $\beta$  show similar biochemical and substrate properties and display high sequence homology, 85% overall and 95% in the catalytic domain.<sup>4</sup> GSK3 was first identified over 20 years ago as one of several kinases that phosphorylates glycogen synthase (GS), the enzyme that catalyzes the last step in glycogen synthesis. This phosphorylation step, in contrast to most signaling pathways, inhibits the action of GS.<sup>5</sup> It was later shown that signaling from the insulin receptor inactivates GSK3 via AKT-catalyzed phosphorylation of serine #9 on the amino terminus of GSK3.<sup>6</sup> Thus, inhibitors of GSK3 would be expected to have some of the same effects as insulin, such as its ability to activate glycogen synthase and stimulate the conversion of glucose to glycogen, thereby lowering plasma glucose. Abnormal regulation of GSK3 has also been demonstrated in insulin resistant rodent and human muscle tissue.<sup>7</sup> Because of these facts, GSK3 has become an attractive target for the potential treatment of NIDDM.<sup>8</sup>

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**Figure 1.** Bis-aryl maleimide GSK3 inhibitors.

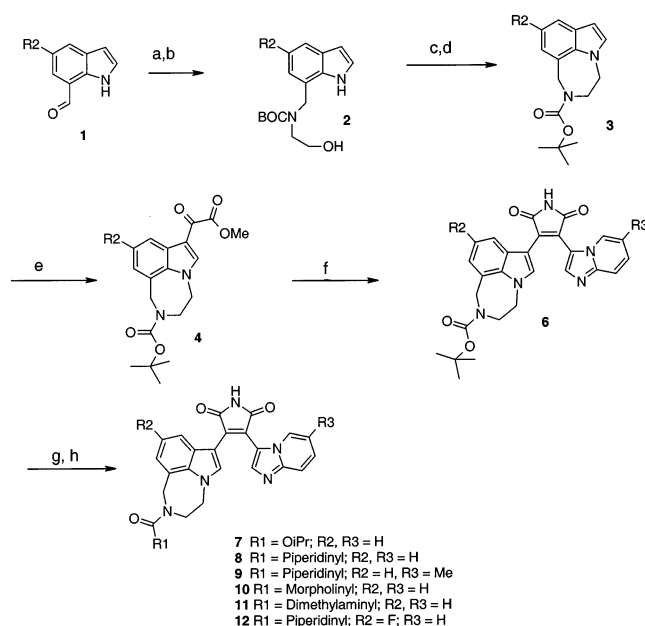
Recently, several groups have reported a variety of bis-aryl maleimide (BAM) inhibitors of GSK3 (Figure 1). BAMs GF 109203x and Ro 31-8220 were shown to inhibit GSK3 with IC<sub>50</sub> values of 170–360 nM and 3–7 nM, respectively, depending on the source of GSK3.<sup>9</sup> SmithKline Beecham reported SB-216763 and SB-415286 to inhibit GSK3- $\alpha$  with an IC<sub>50</sub> of 34 and 77 nM, respectively,<sup>10</sup> while J&J PRD reports a GSK3- $\beta$  IC<sub>50</sub> of 34 nM IC<sub>50</sub> for their macrocyclic BAM.<sup>11a</sup> While the above compounds display varying degrees of GSK3 inhibition, no pharmacokinetic or in vivo efficacy data were presented.<sup>12</sup> Herein we report the results of an effort to develop a new class of orally available and efficacious GSK3 inhibitors, the 3-imidazo[1,2-*a*]pyridin-3-yl-4-(1,2,3,4-tetrahydro-[1,4]diazepino[6,7,1-*h*]indol-7-yl)pyrrole-2,5-diones (**7–12**).

The synthesis of our inhibitors is outlined in Scheme 1. The 1,7-azaannulated indole **3** can be prepared in a four-step process starting with the appropriately substituted 7-formylindole<sup>13,18</sup> (**1**). Reductive amination with ethanolamine and Pd/C gives the desired amino-alcohol which can be protected as the BOC derivative **2**. Activation of the alcohol with mesyl chloride followed by base-induced cyclization gives the desired annulated indole **3** in good yield.<sup>14</sup> Treatment with oxalyl chloride and methanol gives the required oxalate **4**,<sup>14</sup> which can be coupled with the appropriate amide acetamide **5a**<sup>15</sup> or **5b** under basic conditions to give the protected BAM **6**.<sup>16</sup> Removal of the BOC group allows for incorporation of a variety of acyl groups to give **7–12**.

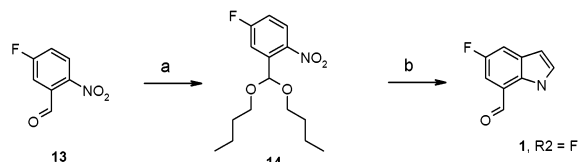
The 5-fluoro-7-formylindole (**1**, R<sub>2</sub> = F) required for the synthesis of **12** can be prepared from **13**<sup>17</sup> via a two-step sequence utilizing the Bartoli indole synthesis<sup>18</sup> as shown in Scheme 2.

The 6-methylimidazopyridine **5b** required for the preparation of compound **9** can be prepared in a two-step process starting with commercial 2-amino-5-methylpyridine as outlined in Scheme 3.

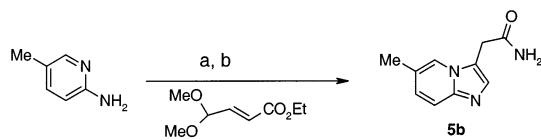
Inhibition of GSK3- $\beta$  by compounds **7–12** was determined in both biochemical and cellular assays. In the biochemical assay, a standard filter binding protocol was used measuring the ability of recombinant GSK3- $\beta$  to phosphorylate phospho-CREB (cAMP response element

Scheme 1<sup>a</sup>

<sup>a</sup> Reagents and conditions (yields for **12**): (a) Ethanolamine, AcOH, NaBH(OAc)<sub>3</sub>, 93%; (b) Boc<sub>2</sub>O, CH<sub>3</sub>CN, 0 °C, 86%; (c) methanesulfonyl chloride, Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C; (d) NaH, DMF, 0 °C, 76% (two steps); (e) oxalyl chloride, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C, then -78 °C, NaOMe, 98%; (f) 2-imidazo[1,2-*a*]pyridin-3-yl-acetamide **5a**, KOT-Bu, THF or DMF; (g) HCl/dioxane, CH<sub>2</sub>Cl<sub>2</sub>, 66% (two steps). (h) carbonyl chloride, MeOH, Et<sub>3</sub>N, rt, 60%.

Scheme 2<sup>a</sup>

<sup>a</sup> Reagents and conditions: (a) *n*-BuOH, TsOH (cat.), toluene, reflux, 95%; (b) vinylmagnesium bromide, THF, -40 °C, then THF, 0.5 N HCl, 55%.

Scheme 3<sup>a</sup>

<sup>a</sup> Reagents and conditions: (a) (*E*)-4,4-Dimethoxy-but-2-enoic acid ethyl ester, CH<sub>3</sub>CN, H<sub>2</sub>O, TsOH, reflux; (b) NH<sub>3</sub>, MeOH, 100 °C, 22% two steps.

binding protein) at serine-129 with ATP[ $\gamma$ -<sup>33</sup>P] in the presence of test compound.<sup>19,20</sup> A similar assay measuring inhibition of GSK3- $\alpha$  was also routinely run, but **7–12** showed no significant ability to discriminate between the two isoforms of GSK3 (data not shown). To the best of our knowledge, no isoform specific inhibitors of GSK3 have been reported, probably due to their high sequence homology (vide supra). A cellular ELISA (P-Tau) assay measured a test compound's ability to block GSK3- $\beta$  dependent phosphorylation of serine-396 of the Tau protein in SY5Y cells.<sup>21</sup>

It is clear from the data in Table 1 that all compounds are very potent inhibitors of GSK3- $\beta$  in the biochemical assay with IC<sub>50</sub>s ranging from 1 to 5 nM. In contrast, the IC<sub>50</sub> of the standard kinase inhibitor staurosporine is 56 nM. Activities  $\leq 1$  nM are below the limits of

Table 1. Biochemical and Cellular Assay Data<sup>a</sup>

| no.           | GSK3- $\beta$ IC <sub>50</sub> (nM) | P-Tau IC <sub>50</sub> (nM) |
|---------------|-------------------------------------|-----------------------------|
| staurosporine | 56 $\pm$ 6.9                        | NT                          |
| <b>7</b>      | 1.3 $\pm$ 0.5                       | 15 <sup>c</sup>             |
| <b>8</b>      | 2.0 $\pm$ 0.4 <sup>b</sup>          | 1.6 <sup>c</sup>            |
| <b>9</b>      | 5.2 $\pm$ 0.8                       | 41 $\pm$ 26 <sup>b</sup>    |
| <b>10</b>     | 1.3 $\pm$ 0.1 <sup>b</sup>          | 2.6 $\pm$ 0.22              |
| <b>11</b>     | 1.6 $\pm$ 0.3                       | 12 $\pm$ 2.6                |
| <b>12</b>     | 1.1 $\pm$ 0.3                       | 0.7 $\pm$ 0.26              |

<sup>a</sup> Data represent mean values of at least three independent determinations ( $\pm$ SE) unless otherwise noted. <sup>b</sup> *N* = 2. <sup>c</sup> *N* = 1.

Table 2. Kinase Activities for Compounds **7–12** (IC<sub>50</sub>s in  $\mu$ M)

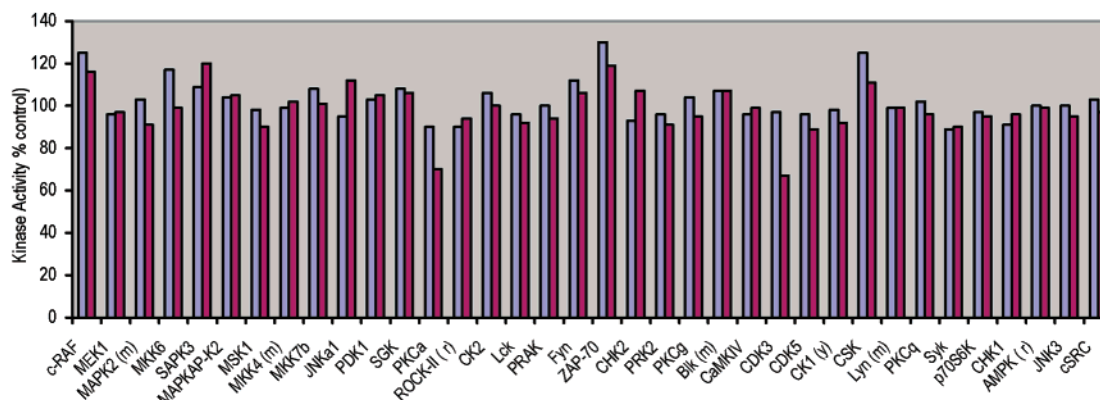
| kinase          | <b>7</b> | <b>8</b> | <b>9</b>        | <b>10</b> | <b>11</b> | <b>12</b> |
|-----------------|----------|----------|-----------------|-----------|-----------|-----------|
| GSK-3 $\beta$   | 0.0013   | 0.002    | 0.0052          | 0.0013    | 0.0016    | 0.0011    |
| Cdk4            | 3.3      | 4.8      | 18              | 1.7       | 1.5       | 1.8       |
| Cdk2            | 3.4      | 5.4      | >20             | 5.3       | 2.1       | 2.8       |
| PKC $\beta$ II  | 0.80     | 0.56     | 0.37            | 1.1       | 1.0       | 0.42      |
| AKT1            | >20      | >20      | >20             | >20       | >20       | >20       |
| PDK-1           | 6.5      | 4.3      | NT <sup>a</sup> | >20       | >20       | 6.2       |
| KDR             | >20      | >20      | >20             | >20       | >20       | >20       |
| TGF $\beta$ -R2 | >20      | 3.1      | 9.5             | 2.0       | >20       | 1.2       |
| hPKA $\beta$    | >20      | >20      | >20             | >20       | >20       | >20       |
| CAMKII          | >20      | >20      | >20             | >20       | 2.5       | >20       |
| MLK7            | >20      | >20      | NT              | 13.4      | >20       | >20       |
| p38             | >20      | >20      | >20             | >20       | >20       | >20       |

<sup>a</sup> Not tested.

sensitivity of this assay,<sup>22</sup> and so a more accurate measure of a compound's true potency can be found in the cellular assay. In the P-Tau assay we see a larger differentiation in activities ranging from 0.7 to 41 nM. Compound **9**, bearing a 6-methyl group on the imidazopyridine, is the least potent inhibitor in both assays and is 25-fold less active in the P-Tau assay than the parent **8**. The piperidine (**8**, **12**) and morpholine (**10**) ureas were found to be favored substituents on the aliphatic ring nitrogen over other groups such as *N,N*-dimethylurea (**11**) and the isopropyl carbamate (**7**). Further, fluorine substitution on the 5-position of the indole in **12** resulted in a modest activity enhancement over the parent compound **8**.

The group of inhibitors was then run through a diverse kinase panel to examine their selectivity profiles. As can be seen in Table 2, all compounds are very selective for GSK3. The most cross reactivity occurs with the cyclin dependent kinases cdk2, cdk4, and also with PKC $\beta$ II, although selectivity ratios are still very good even for compounds with the highest cross reactivity.<sup>23</sup> For example, compound **12** shows an IC<sub>50</sub> of 0.42  $\mu$ M against PKC $\beta$ II, but this is still nearly 400-fold less potent than its activity against GSK3- $\beta$ . As a further measure of selectivity, compound **10** was screened against a second panel of 36 kinases at concentrations of 0.1 and 0.5  $\mu$ M, and the results are shown in Figure 2. No cross reactivity was seen at 0.1  $\mu$ M, and only weak activity (>60% of negative control) against PKC $\alpha$  and CDK3 was seen at 0.5  $\mu$ M. Given the potency of **10**, this represents at least a 500-fold selectivity window for GSK3- $\beta$  over this panel of kinases.

After determining their *in vitro* properties, the compounds were subjected to *in vivo* testing using Zucker diabetic fatty (ZDF) rats.<sup>12</sup> The ZDF rat is an offshoot of the Zucker fatty rat model, which displays the marked skeletal muscle insulin resistance of the parent Zucker strain, combined with induction of diabetes at approximately 8 weeks of age due to pancreatic  $\beta$ -cell failure.<sup>24</sup>



**Figure 2.** Kinase specificity for compound **10**. Single point determinations were run in duplicate. Kinase activity is given as percent of negative control at 0.1  $\mu$ M (blue bars) and 0.5  $\mu$ M (red bars). Kinases are of human origin unless otherwise noted. (m) = mouse, (r) = rat, (y) = yeast.

**Table 3.** ZDF Rat in Vivo Efficacy of 7–12

| no. | % glucose reduction @ 10 mg/kg | % of insulin (10 units) response @ 10 mg/kg | TMED (mg/kg)    |
|-----|--------------------------------|---|-----------------|
| 7   | 58                             | 105   | 4.27 $\pm$ 1.14 |
| 8   | 69                             | 124   | 2.22 $\pm$ 0.45 |
| 9   | 37                             | 75  | ND <sup>a</sup> |
| 10  | 78                             | 119   | 1.44 $\pm$ 0.25 |
| 11  | 53                             | 104   | ND <sup>a</sup> |
| 12  | 61                             | 124   | 1.5 $\pm$ 0.3   |

<sup>a</sup> Not determined. The study failed to yield a significant TMED within the dose range tested (0.3–10 mg/kg).

As an initial filter, rats were dosed via oral gavage with 10 mg/kg of the compound of interest and plasma glucose levels were measured 4 h postdose. Percent glucose reduction could then be determined by comparison to vehicle-treated controls. A positive control group was dosed with 10 units of insulin as an internal standard for percent glucose reduction. Due to variability in response rates, we found it valuable to compare a compound's glucose reduction as a percentage of the positive control group insulin response. To select the most potent and efficacious GSK3 inhibitors, 7 day dose–response studies were conducted to determine threshold minimal effective doses (TMEDs). We defined TMED as the dose where a statistically significant reduction of blood glucose was achieved relative to untreated controls, with the further condition that the glucose reduction be at least 50% of the insulin-treated control group.

The results of the ZDF rat studies are given in Table 3. All compounds performed well at the 10 mg/kg dose, with all but one lowering glucose as well as 10 units of insulin. The TMED shows more separation between the compounds and reveals one general trend. The least potent compounds in the P-Tau cellular assay (7, 9, and 11) are also the least efficacious, with only carbamate 7 yielding a significant result. In contrast, the three most potent compounds in the P-Tau assay (8, 10, and 12) gave the best results in the dose response study, showing TMEDs between 1.4 and 2.2 mg/kg.<sup>25</sup> There-

fore, a compound's potency in the P-Tau cellular assay was a reasonable predictor of its oral in vivo efficacy.

Compound **12** was selected for further study in an oral glucose tolerance test. In this dose–response study, ZDF rats were treated with **12** via oral gavage (dose range 0.1–3 mg/kg, qd) with compound for 8 days. On the eighth day, the rats received a 1.25 g/kg glucose challenge, and the animal's blood glucose was measured over a 2 h period. Compound **12** had a TMED of 0.49  $\pm$  0.15 mg/kg in this study, proving to be a very potent orally active agent.

Pharmacokinetic parameters of compounds **9** and **12** were determined in female rats dosed orally at 10 mg/kg and intravenously at 2 mg/kg. As can be seen in Table 4, compound **9** demonstrated oral bioavailability of 45%, while compound **12** gave an oral bioavailability of 23%. The acceptable pharmacokinetic parameters of **9** and **12** would suggest that the superiority of **12** in the ZDF rat study is due primarily to differences in GSK3 activity as reflected in the P-Tau cellular activity.

In conclusion, we have developed a series of novel, highly potent GSK3 inhibitors. These compounds show a high degree of selectivity against both serine/threonine and tyrosine kinases and have been shown to be highly efficacious oral agents for the reduction of blood glucose in the ZDF rat model of NIDDM. Finally, compound **12** has desirable in vivo and pharmacokinetic properties. Additional studies with this compound will be reported in due course.

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**Supporting Information Available:** Synthetic procedures and characterization for compounds 7–12. This mate-

**Table 4.** Pharmacokinetic Parameters of Compounds 9 and 12

| no. | half-life (IV), h | half-life (oral), h | iv clearance (mL/min/kg) | volume of distribution (l) | oral AUC 0–24 h (ng·h/mL) | oral bioavailability |
|-----|-------------------|---------------------|--------------------------|----------------------------|---------------------------|----------------------|
| 9   | 1                 | ND                  | 17                       | 1                          | 4793                      | 45 $\pm$ 4           |
| 12  | 1.1               | 2.8                 | 12                       | 1                          | 3550                      | 23 $\pm$ 4           |

rial is available free of charge via the Internet at <http://pubs.acs.org>.

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- The  $K_i$  of **11** was determined to be 0.38 nM using traditional kinetics and 0.23 nM via Biacore experiments. This compound was also shown to be a tight binding inhibitor, with the IC<sub>50</sub> being dependent on enzyme concentration.
- Cross reactivity with CDKs and PKCs is common for many, but not all, GSK-3 inhibitors. See refs 8b, 8c, and 11.
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- For comparison, the PPAR agonist rosiglitazone has an MED in the range of 1–3 mg/kg in the same ZDF rat assay.

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