



# Facile synthesis of 1*H*-imidazo[1,2-*b*]pyrazoles via a sequential one-pot synthetic approach

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## Full Research Paper

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## Abstract

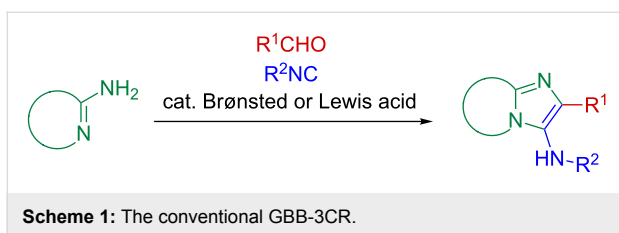
5-Aminopyrazole-4-carbonitrile and ethyl 5-aminopyrazole-4-carboxylate, as potential trifunctional building blocks are introduced in a facile, chemo- and regioselective multicomponent assembly of imidazo[1,2-*b*]pyrazoles via the Groebke–Blackburn–Bienaymé reaction (GBB reaction). Besides the synthetic elaboration of a green-compatible isocyanide-based access in three-component mode, we describe an operationally simple, one-pot two-step GBB protocol for the rapid construction of a 46 membered imidazo[1,2-*b*]pyrazole library with yields up to 83%.

## Introduction

For the relatively rapid design and construction of a diverse, large pharmacophore library, the basic concepts of diversity-oriented synthesis and isocyanide-based multicomponent reactions, such as the Ugi four-component reaction (U-4CR), can be adopted. The sequential combination of four species (amines, aldehydes, isocyanides and carboxylic acids) in a single-pot synthetic operation permits access to bisamide peptidomimetics through a highly electrophilic nitrilium intermediate [1-4]. Modification of the conventional U-4CR protocol in three-component fashion by the incorporation of bifunctional 2-amino-substituted heterocycles provides an alternative

route via an intramolecular *N*-trapping procedure, leading to various *N,N*-heterobicyclic systems [5-12]. A number of bifunctional 2-aminoazoles, including thiazole [13,14] and 1,3,4-thiadiazole [15,16] derivatives, or 2-aminoazine-based heterocycles, such as pyridines [17-19], pyrimidines [20-24] and pyrazines [25-27], have recently been utilized as Groebke–Blackburn–Bienaymé three-component reaction (GBB-3CR) inputs (Scheme 1).

The transformations of either the 5-aminopyrazoles [28,29], or their 4-substituted ethoxycarbonyl [7,30-32] and carbonitrile



[28,33–36] analogues via the GBB-3CR have not been appreciably examined so far. In the relevant literature [7,28,29,31–33], the products have predominantly been described as *5H*-imidazo[1,2-*b*]pyrazoles with an *endo* double bond (and not as *1H*-imidazo[1,2-*b*]pyrazoles), but without 2D NMR-based support. However, the GBB-3CR of functionalized pyrazoles might lead to the formation of two regioisomers [24] and four different tautomeric forms (*5H*- or *1H*-imidazo[1,2-*b*]pyrazole with an *endo*- or *exocyclic* double bond) of each regioisomer. As presented [7,28–36], the “*endo*” *1H*- and *5H*-imidazo[1,2-*b*]pyrazoles were synthesized by the treatment of the corresponding amino substituted pyrazoles with aldehydes and isocyanides in the presence (5–30 mol %) of Lewis or Brønsted acid at ambient temperature or under heating (50–140 °C). The main disadvantages of this protocol involve long reaction times (3–18 hours) and requisite purification protocols (column chromatography and/or recrystallisation) besides limited diversity arising from the pyrazole starting material. As far as we are aware, a one-pot two-step process involving the in situ formation of the desired amino-substituted *N*-heterocycles such as C4 functionalized 5-aminopyrazoles, followed by GBB-3CR has not been described to date.

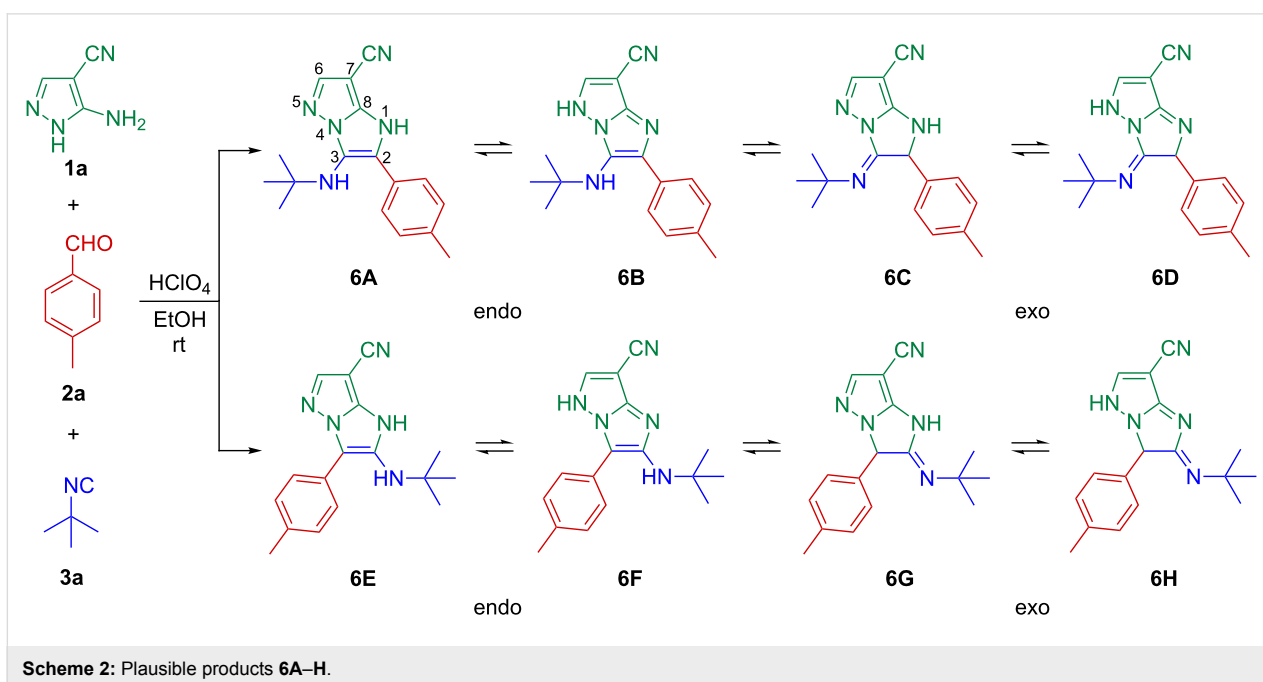
On the other hand, the imidazo[1,2-*b*]pyrazole core is definitely an attractive synthetic target, in view of its noteworthy pharmacological potential, which is strongly affected by the ring substitution pattern and the level of ring saturation. Among others, anti-inflammatory [37,38], antiviral [28,39] and antidiabetic [40] effects should be mentioned, besides the non-negligible cancer cell growth-inhibitory features of the corresponding compounds [30,34,41,42].

With respect to the current requirements of sustainable chemistry, our main aim was to design a streamlined and rapid green synthetic access route to a *1H*-imidazo[1,2-*b*]pyrazole library in sequential one-pot protocol utilizing four components such as hydrazine hydrate, ethoxymethylene substituted malononitrile or ethyl cyanoacetate derivatives, isocyanides and aldehydes.

## Results and Discussion

In the initial stage, a model GBB-3CR was performed between 5-aminopyrazole-4-carbonitrile (**1a**), *p*-tolualdehyde (**2a**) and *tert*-butyl isocyanide (**3a**) in order to elucidate the structure of the product and investigate the regioselectivity. The synthesis of 5-aminopyrazole-4-carbonitrile (**1a**) was based on a literature method [43,44].

A single product was observed in a yield of 59% during a reaction time of 15 min when a catalytic amount of HClO<sub>4</sub> (20 mol %) was used as GBB-3CR promoter [7] in EtOH. 1D- and 2D NMR techniques (<sup>1</sup>H, <sup>13</sup>C-HSQC, <sup>1</sup>H, <sup>13</sup>C-HMBC, <sup>1</sup>H, <sup>1</sup>H-COSY and <sup>1</sup>H, <sup>1</sup>H-NOESY) confirmed the exclusive presence of a *1H*-imidazo[1,2-*b*]pyrazole core with an *endo*-



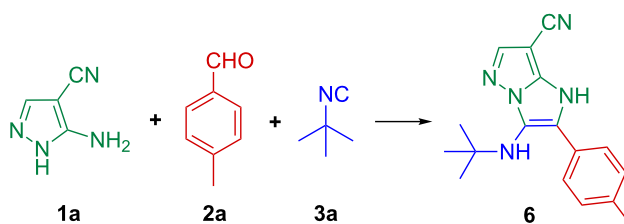
cyclic double bond (**6A**), i.e., without the other possible regioisomeric and tautomeric forms **6B–H** (Scheme 2, see Supporting Information File 1 for detailed data and spectra).

For optimization, the 3CR synthesis of **6** was investigated under different catalytic conditions (Table 1). No reaction occurred in the absence of either a Brønsted or a Lewis acid catalyst (Table 1, entry 1). However, the use of Lewis acids, such as indium(III) salts or TMSCl, improved the reaction rate, with yields up to 67% (Table 1, entries 2–4). The GBB-3CR catalysed by Brønsted acids, including PTSA or HClO<sub>4</sub>, led to similar yields as on Lewis acid catalysis, though better results were obtained by using a catalytic amount of TFA in EtOH (Table 1, entries 5–7). From the aspect of an operationally simple green protocol, a mixture of water and EtOH as reaction medium yielded optimum results in terms of isolated yield, reaction time and mode of isolation (Table 1, entries 7–15). The one-pot 3CR of 5-aminopyrazole-4-carbonitrile (**1a**), *p*-tolu-aldehyde (**2a**) and *tert*-butyl isocyanide (**3a**) catalysed by TFA

(20 mol %) in water/EtOH 1:1 furnished **6** isolated by simple filtration in a yield of 79% during 15 min.

These results led us to envisage a sequential one-pot access to 1*H*-imidazo[1,2-*b*]pyrazole species through the in situ microwave-assisted formation of **1a** followed by a GBB-3CR. A comparative study for the optimum synthesis of **6** revealed that the cyclocondensation of ethoxymethylene malononitrile (**4a**) with hydrazine (**5**) under microwave irradiation (80 °C, 150 W, 10 min, EtOH) proceeded with complete conversion (Scheme 3). It should be mentioned that the presence of water in this step resulted in a complex reaction mixture, moreover, the role of the reagent addition sequence was found to be crucial. The GBB reaction proceeded smoothly with acceptable efficacy during 15 min (overall yield of **6**: 65%), with the addition of water, aldehyde **2a**, a catalytic amount of TFA (20 mol %) and isocyanide **3a** to the solution of the preformed 5-aminopyrazole-4-carbonitrile (**1a**) at room temperature.

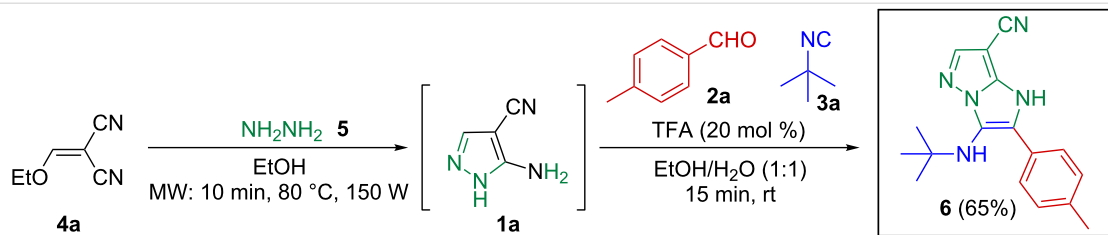
**Table 1:** Solvent and catalyst screen of the GBB-3CR<sup>a</sup>.



Entry	Catalyst	Cat. load (mol %)	Solvent	Reaction time	Yield (%)
1	–	–	EtOH	> 72 h	0
2	In(OTf) <sub>3</sub>	20	EtOH	15 min	61 <sup>b</sup>
3	InCl <sub>3</sub>	20	EtOH	15 min	67 <sup>b</sup>
4	TMSCl	20	EtOH	15 min	64 <sup>b</sup>
5	TsOH·H <sub>2</sub> O	20	EtOH	15 min	52 <sup>b</sup>
6	HClO <sub>4</sub>	20	EtOH	15 min	59 <sup>b</sup>
7	TFA	20	EtOH	15 min	74 <sup>b</sup>
8	TFA	20	CH <sub>2</sub> Cl <sub>2</sub>	15 min	35 <sup>c</sup>
9	TFA	20	CH <sub>2</sub> Cl <sub>2</sub>	20 h	59 <sup>b</sup>
10	TFA	20	CH <sub>2</sub> Cl <sub>2</sub> /MeOH 1:1	15 min	68 <sup>b</sup>
11	TFA	20	MeCN	15 min	68 <sup>b</sup>
12	TFA	20	THF	15 min	74 <sup>b</sup>
13	TFA	20	MeOH	15 min	71 <sup>b</sup>
14	TFA	20	H <sub>2</sub> O	15 min	63 <sup>c</sup>
15	TFA	20	EtOH/H <sub>2</sub> O 1:1	15 min	79 <sup>b</sup>
16	TFA	1	EtOH/H <sub>2</sub> O 1:1	36 h	46 <sup>b</sup>
17	TFA	2	EtOH/H <sub>2</sub> O 1:1	20 h	62 <sup>b</sup>
18	TFA	5	EtOH/H <sub>2</sub> O 1:1	1 h	75 <sup>b</sup>
19	TFA	10	EtOH/H <sub>2</sub> O 1:1	25 min	76 <sup>b</sup>

<sup>a</sup>Reaction conditions: **1a** (0.50 mmol), **2a** (0.55 mmol), **3a** (0.55 mmol), solvent (1 mL), room temperature. <sup>b</sup>Isolated yield after simple filtration.

<sup>c</sup>Isolated yield after flash chromatography.

Scheme 3: Synthesis of **6** via the sequential one-pot method.

The well-established sequential one-pot protocol was then adopted to synthesize a series of 1*H*-imidazo[1,2-*b*]pyrazoles from selected aldehydes **2a–j** and isocyanide building blocks **3a–d** (Table 2). Following the microwave-assisted rapid forma-

tion of **1a**, the one-pot GBB reactions were completed during 10–60 min in yields of 23–83%. Unfortunately, limited substitution effect correlations could be established by employing aromatic aldehydes **2a–h**. The introduction of electron-donating

Table 2: Sequential one-pot GBB library generation<sup>a</sup>.

Entry	R <sup>1</sup> CHO	R <sup>2</sup> NC	Product	Yield (%)	
1	 <b>2a</b>	<i>t</i> -BuNC	<b>3a</b>	<b>6</b>	79 <sup>b,c</sup> (65) <sup>c</sup>
2		<i>t</i> -octyl-NC	<b>3b</b>	<b>7</b>	66 <sup>c</sup>
3		MeOOCCH <sub>2</sub> NC	<b>3c</b>	<b>8</b>	58 <sup>c</sup>
4		CyNC	<b>3d</b>	<b>9</b>	75 <sup>c</sup>
5	 <b>2b</b>	<i>t</i> -BuNC	<b>3a</b>	<b>10</b>	68 <sup>c</sup>
6		<i>t</i> -octyl-NC	<b>3b</b>	<b>11</b>	70 <sup>c</sup>
7		MeOOCCH <sub>2</sub> NC	<b>3c</b>	<b>12</b>	70 <sup>c</sup>
8		CyNC	<b>3d</b>	<b>13</b>	69 <sup>c</sup>
9	 <b>2c</b>	<i>t</i> -BuNC	<b>3a</b>	<b>14</b>	67 <sup>c</sup>
10		<i>t</i> -octyl-NC	<b>3b</b>	<b>15</b>	71 <sup>c</sup>
11		MeOOCCH <sub>2</sub> NC	<b>3c</b>	<b>16</b>	41 <sup>c</sup>
12		CyNC	<b>3d</b>	<b>17</b>	74 <sup>c</sup>
13	 <b>2d</b>	<i>t</i> -BuNC	<b>3a</b>	<b>18</b>	63 <sup>c</sup>
14		<i>t</i> -octyl-NC	<b>3b</b>	<b>19</b>	59 <sup>c</sup>
15		MeOOCCH <sub>2</sub> NC	<b>3c</b>	<b>20</b>	35 <sup>c</sup>
16		CyNC	<b>3d</b>	<b>21</b>	66 <sup>c</sup>
17	 <b>2e</b>	<i>t</i> -BuNC	<b>3a</b>	<b>22</b>	59 <sup>c</sup>
18		<i>t</i> -octyl-NC	<b>3b</b>	<b>23</b>	39 <sup>c</sup>
19		MeOOCCH <sub>2</sub> NC	<b>3c</b>	<b>24</b>	23 <sup>c</sup>
20		CyNC	<b>3d</b>	<b>25</b>	46 <sup>c</sup>
21	 <b>2f</b>	<i>t</i> -BuNC	<b>3a</b>	<b>26</b>	59 <sup>c</sup>
22		<i>t</i> -octyl-NC	<b>3b</b>	<b>27</b>	53 <sup>c</sup>
23		MeOOCCH <sub>2</sub> NC	<b>3c</b>	<b>28</b>	28 <sup>c</sup>
24		CyNC	<b>3d</b>	<b>29</b>	24 <sup>c</sup>

**Table 2:** Sequential one-pot GBB library generation<sup>a</sup>. (continued)

25		<i>t</i> -BuNC	<b>3a</b>	<b>30</b>	53 <sup>c</sup>
26		<i>t</i> -octyl-NC	<b>3b</b>	<b>31</b>	41 <sup>c</sup>
27		MeOOCCH <sub>2</sub> NC	<b>3c</b>	<b>32</b>	33 <sup>c</sup>
28		CyNC	<b>3d</b>	<b>33</b>	46 <sup>c</sup>
29		<i>t</i> -BuNC	<b>3a</b>	<b>34</b>	70 <sup>c</sup>
30		<i>t</i> -octyl-NC	<b>3b</b>	<b>35</b>	83 <sup>c</sup>
31		MeOOCCH <sub>2</sub> NC	<b>3c</b>	<b>36</b>	48 <sup>c</sup>
32		CyNC	<b>3d</b>	<b>37</b>	48 <sup>c</sup>
33		<i>t</i> -BuNC	<b>3a</b>	<b>38</b>	61 <sup>c</sup>
34		<i>t</i> -octyl-NC	<b>3b</b>	<b>39</b>	67 <sup>c</sup>
35		MeOOCCH <sub>2</sub> NC	<b>3c</b>	<b>40</b>	26 <sup>c</sup>
36		CyNC	<b>3d</b>	<b>41</b>	63 <sup>c</sup>
37		<i>t</i> -BuNC	<b>3a</b>	<b>42</b>	50 <sup>d</sup>
38		<i>t</i> -octyl-NC	<b>3b</b>	<b>43</b>	45 <sup>d</sup>
39		MeOOCCH <sub>2</sub> NC	<b>3c</b>	<b>44</b>	47 <sup>d</sup>
40		CyNC	<b>3d</b>	<b>45</b>	40 <sup>d</sup>

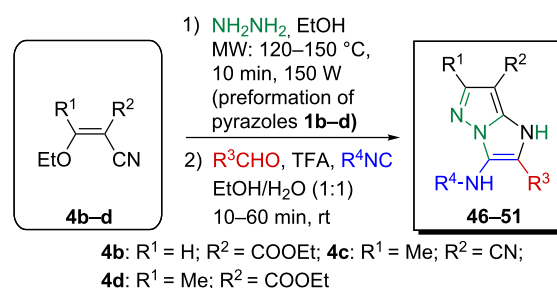
<sup>a</sup>Reaction conditions: **4a** (0.50 mmol), **5** (0.55 mmol), ethanol (0.5 mL), MW (10 min, 80 °C, 150 W), then water (0.5 mL), **2a–j** (0.55 mmol), TFA (0.10 mmol), **3a–d** (0.55 mmol), room temperature, 10–60 min. <sup>b</sup>Isolated yield from the GBB-3CR. <sup>c</sup>Isolated yield after simple filtration. <sup>d</sup>Isolated yield after flash chromatography.

substituents such as 4-Me or 2,4,6-tri-OMe (derived from aldehydes **2a** and **2h**) resulted in similar conversions as for **2b**, whereas the presence of two electron-withdrawing substituents as in **2e–g** resulted in decreased yields.  $\alpha$ -Methylcinnamaldehyde (**2i**) as an uncommon isocyanide-based MCR component was successfully subjected to the GBB reaction, leading to the formation of the corresponding bicycles **38–41** in yields of 26–67%. All the reactions except those based on pivalaldehyde (**2j**) provided access to 1*H*-imidazo[1,2-*b*]pyrazoles through simple filtration. Of the aliphatic isocyanides **3a–d** applied, methyl isocyanoacetate (**3c**) often gave the lowest isolated yields, probably in consequence of self-trapping [45].

To create diversely substituted 1*H*-imidazo[1,2-*b*]pyrazoles, the sequential one-pot GBB method has been extended by means of ethyl 2-cyano-3-ethoxyacrylate (**4b**), (1-ethoxyethylidene) malononitrile (**4c**) and ethyl (*E*)-2-cyano-3-ethoxycrotonate (**4d**). Application of these starting materials in the optimized protocol with a slight modification (elevated temperature was necessary for the microwave assisted preformation of pyrazole intermediates **1b–d**) afforded highly functionalized 1*H*-imidazo[1,2-*b*]pyrazole analogues **46–51** in yields of 54–79% (Table 3).

## Conclusion

We have described here the development of a de novo and facile one-pot, two-step GBB method. The established protocol

**Table 3:** Synthesis of highly substituted 1*H*-imidazo[1,2-*b*]pyrazoles<sup>a</sup>.

Entry	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup> CHO	R <sup>4</sup> NC	Product	Yield <sup>b</sup> (%)
1	H	COOEt	<b>2a</b>	<b>3a</b>	<b>46</b>	54
2	H	COOEt	<b>2b</b>	<b>3b</b>	<b>47</b>	56
3	Me	CN	<b>2a</b>	<b>3a</b>	<b>48</b>	79
4	Me	CN	<b>2c</b>	<b>3c</b>	<b>49</b>	57
5	Me	COOEt	<b>2a</b>	<b>3a</b>	<b>50</b>	74
6	Me	COOEt	<b>2i</b>	<b>3b</b>	<b>51</b>	59

<sup>a</sup>Reaction conditions: **4b–d** (0.50 mmol), **5** (0.55 mmol), ethanol (0.5 mL), MW (10 min; **4b**: 150 °C, **4c,d**: 120 °C; 150 W), then water (0.5 mL), **2a–c,i** (0.55 mmol), TFA (0.10 mmol), **3a–c** (0.55 mmol), room temperature, 10–60 min. <sup>b</sup>Isolated yield after simple filtration.

allowed the rapid synthesis of a 46-membered 1*H*-imidazo[1,2-*b*]pyrazole library with isolated yields up to 83%. Following the microwave-aided formation of functionalized 5-aminopyra-

zoles, the GBB-3CR transformations occurred during 10–60 min under mild conditions. This protocol offers operationally simple, green access to highly substituted 1*H*-imidazo[1,2-*b*]pyrazoles with easily variable substitution pattern and does not require complex purification techniques.

## Supporting Information

### Supporting Information File 1

Experimental and characterisation data.

[<http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-10-243-S1.pdf>]

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## References

- Dömling, A.; Ugi, I. *Angew. Chem., Int. Ed.* **2000**, *39*, 3168–3210. doi:10.1002/1521-3773(20000915)39:18<3168::AID-ANIE3168>3.0.CO;2-U
- Dömling, A. *Chem. Rev.* **2006**, *106*, 17–89. doi:10.1021/cr0505728
- Zhu, J.; Bienaymé, H. *Multicomponent Reactions*; Wiley-VCH: Weinheim, Germany, 2005.
- Kanizsai, I.; Gyónfalvi, S.; Szakonyi, Z.; Sillanpää, R.; Fülöp, F. *Green Chem.* **2007**, *9*, 357–360. doi:10.1039/B613117D
- Groebke, K.; Weber, L.; Mehlin, F. *Synlett* **1998**, 661–663. doi:10.1055/s-1998-1721
- Blackburn, C.; Guan, B.; Fleming, P.; Shiosaki, K.; Tsai, S. *Tetrahedron Lett.* **1998**, *39*, 3635–3638. doi:10.1016/S0040-4039(98)00653-4
- Bienaymé, H.; Bouzid, K. *Angew. Chem., Int. Ed.* **1998**, *37*, 2234–2237. doi:10.1002/(SICI)1521-3773(19980904)37:16<2234::AID-ANIE2234>3.0.CO;2-R
- El Kaim, L.; Grimaud, L. *Tetrahedron* **2009**, *65*, 2153–2171. doi:10.1016/j.tet.2008.12.002
- Parchinsky, V. Z.; Koleda, V. V.; Shuvalova, O.; Kravchenko, D. V.; Krasavin, M. *Tetrahedron Lett.* **2006**, *47*, 6891–6894. doi:10.1016/j.tetlet.2006.07.037
- Agrebi, A.; Allouche, F.; Chabchoub, F.; El-Kaim, L.; Alves, S.; Baleizão, C.; Farinha, J. P. *Tetrahedron Lett.* **2013**, *54*, 4781–4784. doi:10.1016/j.tetlet.2013.06.136
- Pereshivko, O. P.; Peshkov, V. A.; Ermolat'ev, D. S.; Van der Eycken, E. V. *Synlett* **2013**, *24*, 351–354. doi:10.1055/s-0032-1317986
- Guchhait, S. K.; Madaan, C. *Tetrahedron Lett.* **2011**, *52*, 56–58. doi:10.1016/j.tetlet.2010.10.143
- Adib, M.; Mahdavi, M.; Noghani, M. A.; Mirzaei, P. *Tetrahedron Lett.* **2007**, *48*, 7263–7265. doi:10.1016/j.tetlet.2007.08.049
- Sharma, A.; Li, H.-y. *Synlett* **2011**, 1407–1412. doi:10.1055/s-0030-1260568
- Krasavin, M.; Tsurulnikov, S.; Nikulnikov, M.; Kysil, V.; Ivachtchenko, A. *Tetrahedron Lett.* **2008**, *49*, 5241–5243. doi:10.1016/j.tetlet.2008.06.113
- Krasavin, M.; Tsurulnikov, S.; Nikulnikov, M.; Sandulenko, Y.; Bukhryakov, K. *Tetrahedron Lett.* **2008**, *49*, 7318–7321. doi:10.1016/j.tetlet.2008.10.046
- Rousseau, A. L.; Matlaba, P.; Parkinson, C. J. *Tetrahedron Lett.* **2007**, *48*, 4079–4082. doi:10.1016/j.tetlet.2007.04.008
- Shaabani, A.; Soleimani, E.; Maleki, A. *Tetrahedron Lett.* **2006**, *47*, 3031–3034. doi:10.1016/j.tetlet.2006.03.011
- Sandulenko, Y.; Komarov, A.; Rufanov, K.; Krasavin, M. *Tetrahedron Lett.* **2008**, *49*, 5990–5993. doi:10.1016/j.tetlet.2008.07.177
- Parchinsky, V. Z.; Shuvalova, O.; Ushakova, O.; Kravchenko, D. V.; Krasavin, M. *Tetrahedron Lett.* **2006**, *47*, 947–951. doi:10.1016/j.tetlet.2005.11.152
- Carballares, S.; Cifuentes, M. M.; Stephenson, G. A. *Tetrahedron Lett.* **2007**, *48*, 2041–2045. doi:10.1016/j.tetlet.2006.11.181
- Mandair, G. S.; Light, M.; Russel, A.; Horsthouse, M.; Bradley, M. *Tetrahedron Lett.* **2002**, *43*, 4267–4269. doi:10.1016/S0040-4039(02)00709-8
- Umkehrer, M.; Ross, G.; Jäger, N.; Burdack, C.; Kolb, J.; Hu, H.; Alvim-Gaston, M.; Hulme, C. *Tetrahedron Lett.* **2007**, *48*, 2213–2216. doi:10.1016/j.tetlet.2007.01.061
- Thompson, M. J.; Hurst, J. M.; Chen, B. *Synlett* **2008**, 3183–3187. doi:10.1055/s-0028-1087274
- Blackburn, C. *Tetrahedron Lett.* **1998**, *39*, 5469–5472. doi:10.1016/S0040-4039(98)01113-7
- Blackburn, C.; Guan, B. *Tetrahedron Lett.* **2000**, *41*, 1495–1500. doi:10.1016/S0040-4039(00)00003-4
- Shaabani, A.; Soleimani, E.; Maleki, A.; Moghimi-Rad, J. *Synth. Commun.* **2008**, *38*, 1090–1095. doi:10.1080/00397910701862931
- Elleder, D.; Young, J. A. T.; Baiga, T. J.; Noel, J. P. Non-nucleoside Reverse Transcriptase Inhibitors. WO Patent 2009/061856 A1, May 14, 2009.
- Gerlach, M.; Maul, C. Bicyclic Imidazo-5-yl-amine Derivatives. U.S. Patent 2002/0183320 A1, Dec 5, 2002.
- Baviskar, A. T.; Madaan, C.; Preet, R.; Mohapatra, P.; Jain, V.; Agarwal, A.; Guchhait, S. K.; Kundu, C. N.; Banerjee, U. C.; Bharatam, P. V. *J. Med. Chem.* **2011**, *54*, 5013–5030. doi:10.1021/jm200235u
- Guchhait, S. K.; Madaan, C.; Thakkar, B. S. *Synthesis* **2009**, 3293–3300. doi:10.1055/s-0029-1216916
- Guchhait, S. K.; Madaan, C. *Synlett* **2009**, 628–632. doi:10.1055/s-0028-1087915
- Rahmati, A.; Kouzehrash, M. A. *Synthesis* **2011**, 2913–2920. doi:10.1055/s-0030-1260154
- Zhang, J.; Singh, R.; Goff, D.; Kinoshita, T. Small Molecule Inhibitors of Spleen Tyrosine Kinase (SYK). U.S. Patent 2010/0316649 A1, Dec 16, 2010.
- Rahmati, A.; Eskandari-Vashareh, M.; Alizadeh-Kouzehrash, M. *Tetrahedron* **2013**, *69*, 4199–4204. doi:10.1016/j.tet.2013.03.103
- Budd, D.; Qian, Y.; Schoenfeld, R. C.; Sidduri, A. Lpar - substituted cyanopyrazole compounds. WO Patent 2014/037303 A1, March 13, 2014.
- Bruno, O.; Brullo, C.; Bondavalli, F.; Ranise, A.; Schenone, S.; Falzarano, M. S.; Varanic, K.; Spisani, S. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 3696–3701. doi:10.1016/j.bmcl.2007.04.036

38. Terada, A.; Wachi, K.; Miyazawa, H.; Iizuka, Y.; Hasegawa, K.; Tabata, K. Use of Imidazopyrazole Derivates as Analgesics and Anti-inflammatory Agents. U.S. Patent 5,232,939, Aug 3, 1993.
39. Frey, B.; Hufton, R.; Harding, M.; Draffan, A. G. Compounds for the Treatment of HCV. WO Patent 2013/036994 A1, March 21, 2013.
40. Mascitti, V.; McClure, K. F.; Munchhof, M. J.; Robinson, R. P. Imidazo-pyrazoles as Gpr119 Inhibitors. WO Patent 2011/061679 A1, May 26, 2011.
41. Ennis, H. L.; Möller, L.; Wang, J. J.; Selawry, O. S. *Biochem. Pharmacol.* **1971**, *20*, 2639–2646. doi:10.1016/0006-2952(71)90173-0
42. Oku, T.; Kawai, Y.; Marusawa, H.; Yamazaki, H.; Abe, Y.; Tanaka, H. E. 3-(heteroaryl)-pyrazolol[1,5-*a*]pyrimidines. U.S. Patent 5,356,897, Oct 18, 1994.
43. Reidlinger, C.; Dworzak, R.; Junek, H.; Graubaus, H. *Monatsh. Chem.* **1998**, *129*, 1313–1318. doi:10.1007/PL00010144
44. Tarabová, D.; Šoralová, S.; Breza, M.; Fronc, M.; Holzer, W.; Milata, V. *Beilstein J. Org. Chem.* **2014**, *10*, 752–760. doi:10.3762/bjoc.10.70
45. Lalli, C.; Bouma, M. J.; Bonne, D.; Masson, G.; Zhu, J. *Chem. – Eur. J.* **2011**, *17*, 880–889. doi:10.1002/chem.201002098

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