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Research Article

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Design of a Versatile Multicomponent Reaction Leading to 2-amino-5-ketoaryl pyrroles

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The design of an unprecedented multicomponent reaction to and synthesis of 2-amino-5-ketoaryl pyrroles are described. The compounds (14 examples) can be synthesized by reacting aminoacetophenone sulfonamides, (hetero)aromatic aldehydes, and malonodinitrile or cyanoacetic acid derivatives in one-pot manner. Pharmacophore features and potential applications of this new scaffold are discussed.

Key words: 2-aminopyrrole, aminoacetophenone sulfonamides, cyanoacetamides, multicomponent reaction

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Introduction

The 2-aminopyrrole fragment is part of many different bioactive compounds. Reported bioactivities include, IL-6 production inhibition (1), IκB kinase β inhibition (2), intergrin antagonists (3), signal transduction modulators (4), antitumor (5), and antibacterial (6), just to name a few. For example, a RELIBASE search of the Protein Data Bank for the 2-aminopyrrole fragment results in 79 ligand hits (7). Notably, the 2-aminopyrrole chemotype is planar and comprise two adjacent hydrogen bond donor or alternatively hydrogen bond donor and acceptor moieties, respectively, dependent on the protonation state to interact with a protein target (Figure 1). Additionally, the flat pyrrole ring system contributes to its extraordinary chemotype and is the prerequisite to enter narrow and deep binding pockets in target proteins. The reported kinase activity of certain 2-aminopyrroles can certainly be attributed to this two pharmacophore features. Pyrroles comprise electron-rich heteroaromates and can therefore undergo favorable π–π interactions in proteins as exemplified in the interaction with Phe97 in Figure 2. Additionally, the 2-aminopyrrole moiety comprises a heterocycle-encompassed amidine with reduced basicity, higher electron delocalization, and thus potentially better penetration through biological membranes.

In Figure 2, two representative molecular interactions of small molecular weight 2-aminopyrrole moieties with a protein target are depicted. Key interactions involve the pyrrole-NH in hydrogen bond acceptors, e.g. Asn112 and Tyr174. Thus, 2-aminopyrroles are interesting synthetic targets to obtain biologically active compounds. Therefore, new synthetic routes toward this chemotype are of demand. Herein, we would like to report the discovery of a versatile 3-component reaction leading to 2-amino-5-ketoaryl pyrroles.

Pyrroles can be synthesized by a variety of classical and new multicomponent reactions (MCRs), including the Piloty–Robinson reaction (2 equiv. aldehyde and hydrazine) (8,9), an *in situ* coupling–isomerization Stetter–Paal–Knorr variant (10), and the 3-CR of amino acids, acylchlorides and dimethyl acetylenedicarboxylate (DMAD) (11), a 3-CR of *N*-tosylimines, DMAD, and isocyanides (12), in addition to classical synthesis such as the Paal–Knorr reaction (13,14). The use of malondinitrile to form 5-membered ring cyclic adducts, e.g. aminopyrrole, has been reported (15). We recently described an operationally simple, efficient, and cheap access to cyanoacetamides derived from methyl cyanoacetate and primary or secondary aliphatic amines (16). This procedure allows us to synthesize many different diversely substituted cyanoacetamides. Cyanoacetamides are electronically activated methylene compounds, and regarding their reactivity, they are related to malonodinitrile, which shows a very versatile and interesting MCR chemistry (for a recent comprehensive review, see 17). Having access to such a diversity of starting materials, we became interested in the design of new MCRs based on these starting materials. Our design consideration for the herein disclosed MCR was as follows.

The versatile chemistry of toluenesulfonylmethyl isocyanide (Tosmic) leading to pyrroles, imidazoles, and other heterocycles, according to van Leusen, is critically dependent on the multifunctionality of the Tosmic reagent (Figure 3). It incorporates strong α-acidity, an *N,S*-acetale, the isocyanide moiety and the leaving group sulfinic acid. The later property is crucial for the final aromatization of the intermediate pyrrolidines and imidazolidines.

Thus, we intended to introduce an α-acidic reagent featured with a leaving group (Ts) into malonodinitrile to test whether MCRs can be performed incorporating a sulfinic acid elimination with concomitant aromatization (Scheme 1).

Experimental Section

General procedure for 3-component reaction of aminoacetophenone sulfonamides, (hetero) aromatic aldehydes, and malonodinitrile or cyanoacetic acid derivatives: Add aldehyde (1.0 equiv.), aminoacetophenone sulfonamide (1.0 equiv.), malonodinitrile or cyanoacetic acid derivatives (1.0 equiv.), triethylamine (1.0 equiv.), and 2,2,2-triflu-

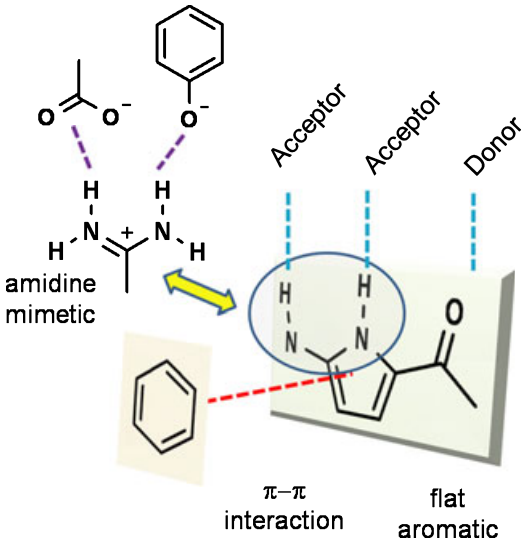


Figure 1: Pharmacophore features of the 2-aminopyrrole moiety.

oroethanol (0.2 M) in a 20-mL vial with a stir bar. The reaction was allowed to heat to 70 °C in an oil bath for 12 h. Then, the reaction was cooled down to 0 °C to yield a precipitate that is filtered. The solid is washed with cold ethanol and dried in an oven to yield the desired products as light yellow solid. In some cases where no precipitate appears, the target products were purified by silica gel chromatography. (For copies of the 1H and 13C NMR data see Data S1, Supporting Information.)

2-Amino-5-benzoyl-4-(4-chlorophenyl)-1H-pyrrole-3-carbonitrile (D1)

HRMS ESI-TOF for $C_{18}H_{12}ClN_3O$ (M^+) found: *m/z*: 321.0658; Calc. Mass 321.0669. ^1H NMR (d_6-DMSO (dimethyl sulphoxide), 600 MHz): 6.47 (s, 2H), 7.02 (d, J = 7.8 Hz, 2H), 7.08 (t, J = 7.2 Hz, 2H), 7.12 (d, J = 8.4 Hz, 2H), 7.25 (d, J = 7.2 Hz, 2H), 7.28 (t, J = 7.2 Hz, 1H), 11.14 (s, 1H) ppm; ^{13}C NMR (d_6-DMSO, 150 MHz): 116.5, 121.0, 127.9, 128.0, 129.0, 131.1, 131.8, 131.9, 132.7, 134.5, 138.7, 150.9, 183.9 ppm.

Methyl 2-amino-5-benzoyl-4-(4-chlorophenyl)-1H-pyrrole-3-carboxylate (D2)

HRMS ESL-TOF for $C_{19}H_{15}ClN_2O_3$ (M^+) found: *m/z*: 354.0762; Calc. Mass 354.0771. ^1H NMR (d_6-DMSO, 600 MHz): 3.46 (s, 3H), 6.23 (s, 2H), 6.92–6.96 (m, 4H), 7.01 (s, 2H), 7.12 (s, 2H), 7.21 (s, 1H), 10.95 (s, 1H) ppm; ^{13}C NMR (d_6-DMSO, 150 MHz): 50.6, 96.0, 122.3, 126.7, 127.6, 128.6, 130.2, 131.7, 132.9, 133.2, 133.6, 139.3, 150.0, 165.3, 184.8, ppm.

(5-Amino-3-(4-chlorophenyl)-4-(pyrrolidine-1-carbonyl)-1H-pyrrol-2-yl)(phenyl)methanone (D3)

HRMS ESL-TOF for $C_{22}H_{20}ClN_3O_2$ (M^+) found: *m/z*: 393.1235; Calc. Mass 393.1244. ^1H NMR (d_6-DMSO, 600 MHz): 1.55 (s, 4H), 3.10 (brs, 4H), 5.58 (s, 2H), 6.88 (d, J = 7.2 Hz, 2H), 7.00 (d, J = 7.2 Hz, 2H), 7.05 (t, J = 7.2 Hz, 2H), 7.18 (d, J = 7.8 Hz, 2H), 7.23 (t, J = 6.6 Hz, 1H), 10.80 (s, 1H), ppm; ^{13}C NMR (d_6-DMSO, 150 MHz):

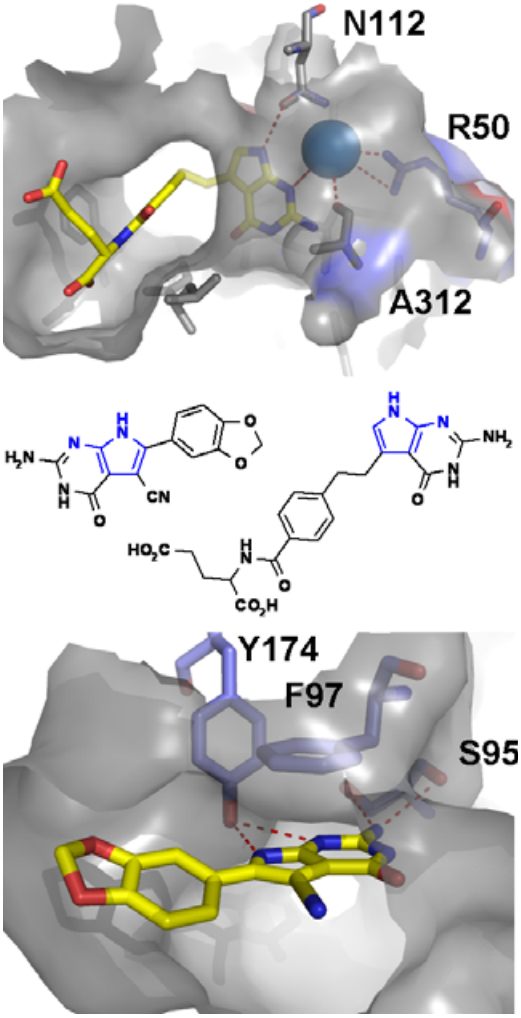


Figure 2: Interaction motifs of the 2-aminopyrrole with two different molecular targets. Top: X-ray crystal structure of a pyrrolo(2,3-d)pyrimidine-based antifolate (yellow sticks) in complex with human thymidylate synthetase (gray surface) (pdb identifier: 1JU6). The 2-aminopyrrole moiety is involved in an extended hydrogen bond network of Asn112 and a water molecule (marine blue ball), which mediates other hydrogen bond contacts to Arg50 and Ala312. Bottom: Pyrrole inhibitor (yellow sticks) with the pteridine reductase 1 (PRT1) (gray surface) from the parasite *Trypanosoma brucei* (pdb identifier: 3BML). The hydrogen bond network interaction of the 2-aminopyrrole moiety with Tyr174 and Ser95 is highlighted (red dotted lines). Noteworthy also is the $\pi-\pi$ interaction of the ligand planar pyrrole ring with the phenyl group of Phe97. Rendering software PyMol is used.

9.1, 21.2, 46.2, 104.3, 120.1, 126.0, 127.6, 127.7, 128.5, 128.8, 130.2, 131.7, 131.8, 131.9, 134.0, 139.9, 145.4, 164.9, 183.2 ppm.

2-Amino-5-benzoyl-N-butyl-4-(4-chlorophenyl)-1H-pyrrole-3-carboxamide (D4)

HRMS ESL-TOF for $C_{22}H_{22}ClN_3O_2$ (M^+) found: *m/z*: 395.1397; Calc. Mass 395.1401. ^1H NMR (d_6-DMSO, 600 MHz): 0.71 (t, J = 7.2 Hz,

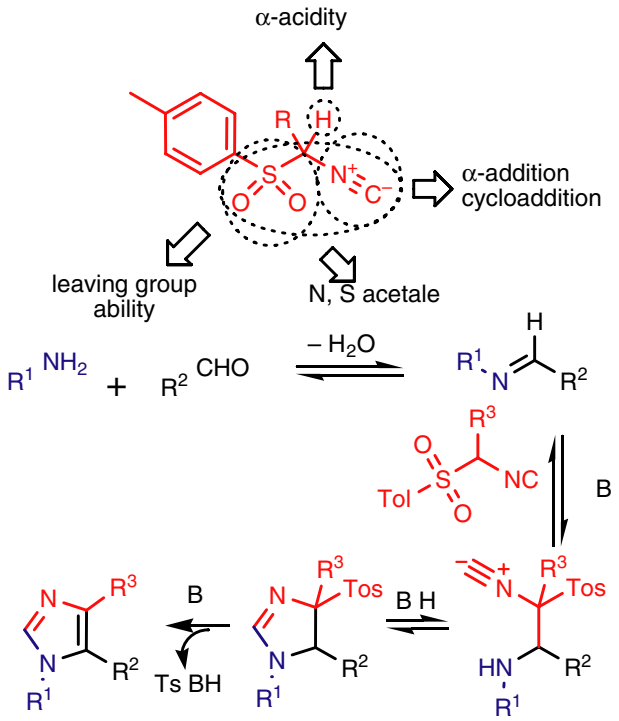
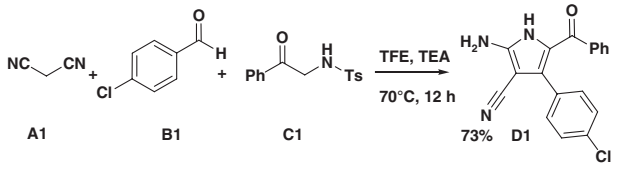


Figure 3: Reactivity of Tosmic and the mechanism of Van Leuson reaction. The basic elimination of Tos in the last step produces the aromatic heterocycle.



Scheme 1: The new 3-CR of (hetero)aromatic aldehydes, malondinitrile or cyanoacetic acid derivatives, and aminoacetophenone sulfonamides.

3H), 0.90 (pent, J = 7. 8 Hz, 2H), 1.07 (pent, J = 7.2 Hz, 2H), 2.95 (q, J = 6.0 Hz, 1H), 5.09 (t, J = 5.4 Hz, 1H), 6.25 (s, 2H), 7.02 (t, J = 8.4 Hz, 2H), 7.03 (d, J = 8.4 Hz, 2H), 7.12 (d, J = 8.4 Hz, 4H), 7.20 (t, J = 7.2 Hz, 1H), 10.94 (s, 1H), ppm; ^{13}C NMR (d_6-DMSO, 150 MHz): 13.3, 19.2, 30.6, 37.5, 99.5, 120.8, 127.1, 127.6, 127.8, 129.3, 130.3, 132.2, 132.3, 132.8, 139.2, 164.8, 183.4 ppm.

2-Amino-5-benzoyl-N-benzyl-4-(naphthalen-1-yl)-1H-pyrrole-3-carboxamide (D5)

HRMS ESL-TOF for $C_{29}H_{23}N_3O_2$ (M^+) found: *m/z*: 445.1769; Calc. Mass 445.1790. ^{1}H NMR (d_6-DMSO, 600 MHz): 3.81 (dd, J = 15.6, 4.8 Hz, 1H), 4.05 (dd, J = 15.6, 6.6 Hz, 1H), 5.09 (t, J = 6.0 Hz, 1H), 6.90 (d, J = 8.4 Hz, 2H), 6.92 (t, J = 7.8 Hz, 1H), 6.98 (t, J = 7.8 Hz, 2H), 7.05 (t, J = 7.2 Hz, 1H), 7.10 (t, J = 7.8 Hz, 1H), 7.14 (d, J = 6.6 Hz, 1H), 7.48–7.52 (m, 2H), 7.62 (d, J = 7.8 Hz, 1H), 7.69 (t, J = 4.8 Hz, 1H), 7.81 (t, J = 4.8 Hz, 1H), 11.09 (s, 1H) ppm; ^{13}C NMR (d_6-DMSO, 150 MHz): 41.5, 99.8, 121.8, 124.8, 125.2, 125.9, 126.0, 126.3, 126.6, 127.9, 127.9, 128.1, 128.7, 129.0, 129.1, 131.2, 132.2, 132.8, 138.0, 139.2, 149.2, 164.9, 183.7 ppm.

2-Amino-5-benzoyl-N-benzyl-4-(4-fluorophenyl)-1H-pyrrole-3-carboxamide (D6)

HRMS ESL-TOF for $C_{25}H_{20}FN_3O_2$ (M^+) found: *m/z*: 413.1530; Calc. Mass 413.1540. ^{1}H NMR (d_6-DMSO, 600 MHz): 4.17 (d, J = 6.0 Hz, 2H), 5.52 (t, J = 5.4 Hz, 1H), 6.29 (s, 2H), 6.79 (t, J = 9.0 Hz, 2H), 6.95 (d, J = 7.8 Hz, 2H), 7.01 (t, J = 7.2 Hz, 2H), 7.04 (dd, J = 7.8, 5.4 Hz, 2H), 7.11 (d, J = 7.8 Hz, 2H), 7.18 (t, J = 7.8 Hz, 2H), 7.22 (t, J = 6.6 Hz, 2H), 10.95 (s, 1H) ppm; ^{13}C NMR (d_6-DMSO, 150 MHz): 42.5, 99.9, 115.2 (d, J = 21 Hz), 121.6, 127.2, 127.4, 127.6, 128.3, 128.6, 129.9, 130.4 (d, J = 3 Hz), 131.1, 133.0 (d, J = 9 Hz), 139.2, 139.7, 149.3, 161.9 (d, J = 243 Hz), 165.5, 184.2, ppm.

2-Amino-5-benzoyl-N-cyclopropyl-4-(pyridin-4-yl)-1H-pyrrole-3-carboxamide (D7)

HRMS ESL-TOF for $C_{20}H_{18}N_4O_2$ (M^+) found: *m/z*: 346.1435; Calc. Mass 346.1430. ^{1}H NMR (d_6-DMSO, 600 MHz): –0.28 to –0.18 (m, 2H), 0.47–0.48 (m, 2H), 2.47 (m, 1H), 5.48 (s, 1H), 6.13 (s, 2H), 6.97 (d, J = 6.0 Hz, 2H), 7.03 (t, J = 7.8 Hz, 2H), 7.16 (d, J = 7.2 Hz, 2H), 7.21 (t, J = 7.8 Hz, 1H), 8.21 (s, 2H), 11.03 (s, 1H), ppm; ^{13}C NMR (d_6-DMSO, 150 MHz): 6.4, 22.4, 100.4, 120.9, 126.1, 127.7, 128.4, 129.6, 130.5, 139.6, 142.7, 148.6, 149.0, 166.3, 184.0 ppm.

2-Amino-5-benzoyl-N-butyl-4-(pyridin-2-yl)-1H-pyrrole-3-carboxamide (D8)

HRMS ESI-TOF (High resolution mass spectrometry using electron spray ionization and time of flight): for $C_{21}H_{22}N_4O_2$ (M^+) found *m/z*: 362.1747, Calc. Mass 362.1743. ^{1}H NMR (d_6-DMSO, 600 MHz): 0.76 (t, J = 7.8 Hz, 3H), 1.00–1.10 (m, 2H), 1.25 (pent, J = 7.2 Hz, 2H), 3.07 (q, J = 6.0 Hz, 2H), 6.30 (s, 2H), 6.81 (d, J = 7.8 Hz, 1H), 7.02 (t, J = 7.8 Hz, 2H), 7.09–7.13 (m, 1H), 7.14–7.20 (m, 4H), 8.16 (t, J = 5.4 Hz, 1H), 8.55 (d, J = 4.8 Hz, 1H), 11.07 (s, 1H) ppm; ^{13}C NMR (d_6-DMSO, 150 MHz): 13.4, 19.3, 30.7, 37.5, 99.2, 121.6, 122.4, 127.2, 128.1, 128.4, 129.5, 129.9, 135.8, 139.1, 147.7, 148.8, 153.3, 165.2, 183.5 ppm.

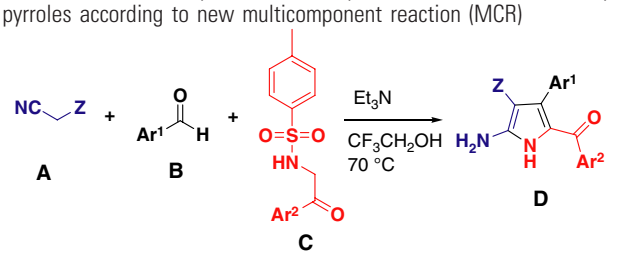
2-Amino-N-benzyl-5-(4-bromobenzoyl)-4-(4-chloro-2-hydroxyphenyl)-1H-pyrrole-3-carboxamide (D9)

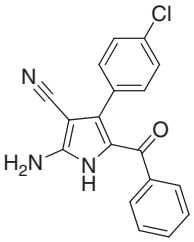
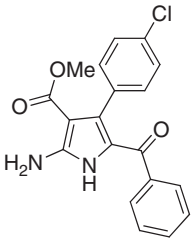
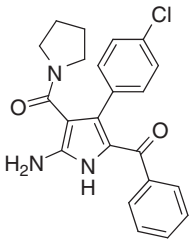
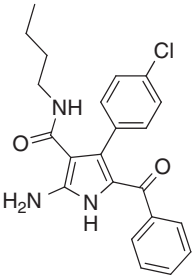
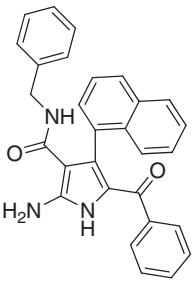
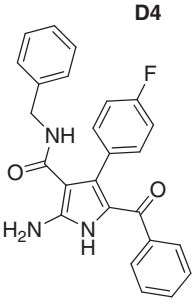
HRMS ESL-TOF for $C_{25}H_{19}BrClN_3O_3$ (M^+) found: *m/z*: 523.0295; Calc. Mass 523.0298. ^{1}H NMR (d_6-DMSO, 600 MHz): 4.17 (dd, J = 14.4, 6.6 Hz, 1H), 4.24 (dd, J = 14.4, 6.6 Hz 1H), 5.77 (t, J = 5.4 Hz, 1H), 6.29 (s, 2H), 6.49 (dd, J = 7.8, 1.8 Hz, 1H), 6.59 (d, J = 1.8 Hz, 1H), 6.71 (d, J = 8.4 Hz, 1H), 6.93 (s, J = 7.2 Hz, 1H), 7.07 (d, J = 8.4 Hz, 1H), 7.16–7.24 (m, 5H), 10.11 (s, 1H), 10.96 (s, 1H) ppm; ^{13}C NMR (d_6-DMSO, 150 MHz): 42.5, 115.7, 119.1, 120.5, 121.5, 123.4, 127.1, 127.2, 128.1, 128.6, 129.7, 130.3, 133.6, 134.0, 139.0, 139.1, 149.7, 156.4, 165.7, 182.7 ppm.

Triethylammonium 2-amino-5-benzoyl-4-(4-chlorophenyl)-1H-pyrrole-3- carboxylate (D10)

^{1}H NMR (d_6-DMSO, 600 MHz): 1.14 (t, J = 7.2 Hz, 9H), 3.07 (q, J = 7.2 Hz, 6H), 6.94 (d, J = 8.4 Hz, 2H), 7.06 (d, J = 8.4 Hz, 2H),

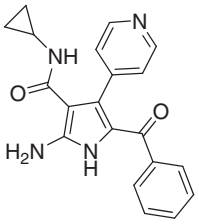
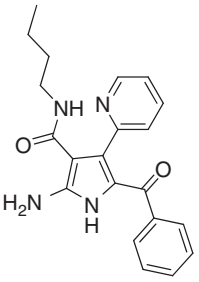
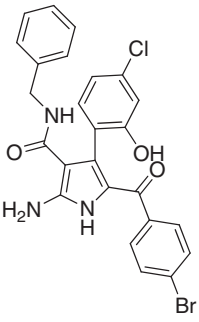
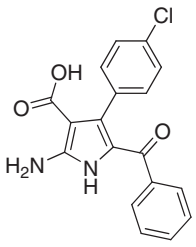
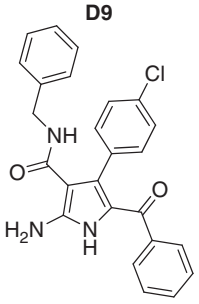
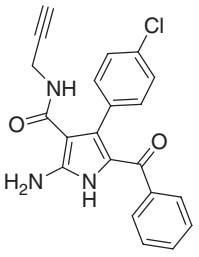
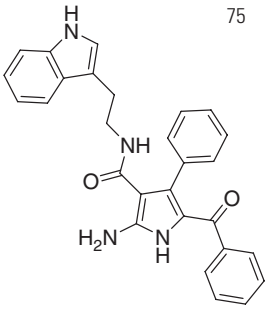
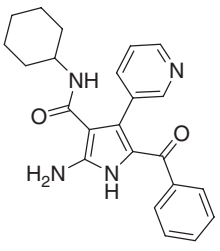
Table 1: Isolated yields of the synthesized 2-amino-5-ketoaryl pyrroles according to new multicomponent reaction (MCR)



Yield	Structure	Yield	Structure
73	 **D1**	45	 **D2**
48	 **D3**	51	 **D4**
65	 **D5**	57	 **D6**

D6

Table 1: (Continued)

Yield	Structure	Yield	Structure
62	 **D7**	67	 **D8**
60	 **D9**	32	 **D10**
64	 **D11**	44	 **D12**
32	 **D13**	75	 **D14**

Et3N.

7.08 (t, J = 7.8 Hz, 2H), 7.24 (d, J = 8.4 Hz, 2H), 7.27 (t, J = 7.8 Hz, 1H), 8.98 (s, 1H), 9.39 (s, 1H), 10.89 (s, 1H) ppm; ^{13}C NMR (d_6-DMSO, 150 MHz): 9.1, 46.2, 122.2, 123.8, 126.4, 127.8, 128.6, 129.0, 130.8, 131.4, 133.0, 133.5, 139.2, 164.8, 176.5, 186.1 ppm.

2-Amino-5-benzoyl-N-benzyl-4-(4-chlorophenyl)-1H-pyrrole-3-carboxamide (D11)

HRMS ESL-TOF for $C_{25}H_{20}ClN_3O_2$ (M^+) found: *m/z*: 429.1247, calc. Mass 429.1244. ^{1}H NMR (d_6-DMSO, 600 MHz): 4.18 (s, 2H), 5.61 (t, J = 5.4 Hz, 1H), 6.25 (s, 2H), 6.93 (d, J = 7.2 Hz, 2H), 6.99–7.04 (m, 6H), 7.11 (d, J = 7.2 Hz, 2H), 7.19 (d, J = 7.2 Hz, 2H), 7.21 (d, J = 7.2 Hz, 2H), 10.96 (s, 1H), ppm; ^{13}C NMR (d_6-DMSO, 150 MHz): 42.6, 100.0, 121.4, 127.2, 127.4, 127.6, 128.1, 128.3, 128.6, 129.9, 130.9, 132.7, 132.8, 133.1, 139.2, 139.7, 149.2, 165.4, 184.1 ppm.

2-Amino-5-benzoyl-4-(4-chlorophenyl)-N-(prop-2-ynyl)-1H-pyrrole-3-carboxamide (D12)

HRMS ESL-TOF for $C_{21}H_{16}ClN_3O_2$ (M^+) found: *m/z*: 377.0934; Calc. Mass 377.0931. ^1H NMR (d_6-DMSO, 600 MHz): 3.04 (s, 1H), 3.82 (s, 2H), 5.56 (s, 1H), 6.31 (s, 2H), 7.05–7.10 (m, 4H), 7.16 (d, J = 7.2 Hz, 2H), 7.18 (d, J = 7.2 Hz, 2H), 7.27 (t, J = 7.2 Hz, 1H), 11.03 (s, 1H), ppm; ^{13}C NMR (d_6-DMSO, 150 MHz): 28.3, 73.3, 81.3, 99.3, 121.5, 127.7, 128.2, 128.4, 130.0, 130.8, 132.8, 132.9, 139.6, 149.3, 165.2, 184.3 ppm.

N-(2-(1H-indol-3-yl)ethyl)-2-amino-5-benzoyl-4-phenyl-1H-pyrrole-3-carboxamide (D13)

HRMS ESL-TOF for $C_{28}H_{24}N_4O_2$ (M^+) found: *m/z*: 448.1903, calc. Mass 448.1899. NMR (d_6-DMSO, 600 MHz): 2.58 (t, J = 6.0 Hz, 2H), 3.30 (q, J = 6.0 Hz, 2H), 5.16 (t, J = 5.4 Hz, 1H), 6.41 (s, 2H), 6.84 (s, 1H), 6.90–7.02 (m, 5H), 7.03 (t, J = 7.2 Hz, 1H), 7.11 (t, J = 7.8 Hz, 1H), 7.14 (d, J = 7.8 Hz, 2H), 7.16 (t, J = 7.2 Hz, 1H), 7.38 (d, J = 7.2 Hz, 2H), 7.41 (d, J = 7.8 Hz, 2H), 10.79 (s, 1H), 10.93 (s, 1H) ppm; ^{13}C NMR (d_6-DMSO, 150 MHz): 25.3, 39.5, 99.6, 111.6, 111.8, 118.5, 118.6, 121.3, 121.4, 123.0, 127.4, 127.5, 127.8, 128.1, 128.2, 129.9, 130.7, 132.1, 134.1, 136.7, 139.7, 149.4, 165.6, 184.1 ppm.

2-Amino-5-benzoyl-N-cyclohexyl-4-(pyridin-3-yl)-1H-pyrrole-3-carboxamide (D14)

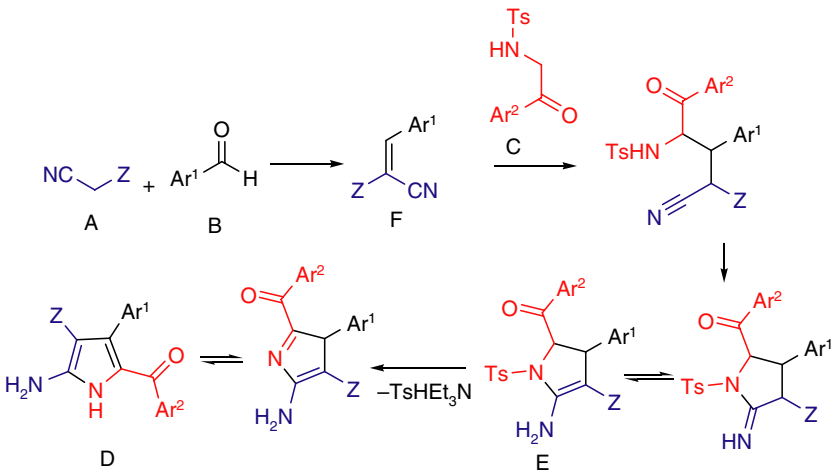
HRMS ESL-TOF for $C_{23}H_{24}N_4O_2$ (M^+) found: *m/z*: 388.1903, calc. Mass 388.1899. NMR (d_6-DMSO, 600 MHz): 0.73–1.51 (m, 10H), 3.53 (s, 1H), 4.94 (s, 1H), 6.23 (s, 2H), 6.98–7.03 (m, 2H), 7.10 (dd, J = 7.8, 2.1 Hz, 1H), 7.13–7.20 (m, 3H), 7.46 (s, 1H), 8.30 (s, 1H), 8.31 (s, 1H), 11.02 (s, 1H) ppm; ^{13}C NMR (d_6-DMSO, 150 MHz): 23.9, 25.4, 32.3, 46.7, 100.5, 121.7, 123.0, 127.8, 128.3, 128.4, 130.2, 130.6, 138.3, 139.5, 148.6, 149.2, 151.0, 164.4, 184.0 ppm.

Results and Discussion

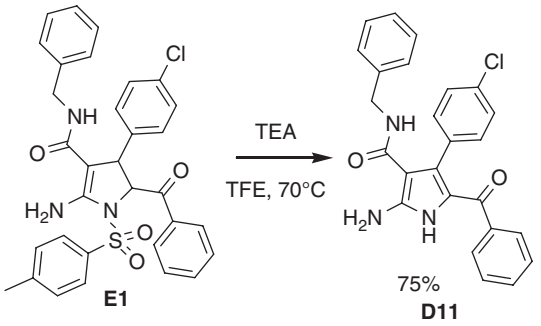
Thus, we synthesized aminoacetophenone sulfonamides according to known procedures that should be spiked with both chemical properties, α-acidity and leaving group ability (18,19). The key and primary step in malonodinitrile chemistry is the Knoevenagel condensation with oxocomponent. Thus, we mixed aminoacetophenone sulfonamide, *para*-chlorobenzaldehyde, and malonodinitrile in the presence of triethylamine (TEA). After 12 h of reflux in trifluoroethanol (TFE) a solid precipitated, which to our own surprise consisted of the 2-aminopyrrole (**D1**) as confirmed by NMR and HR-MS.

Next, we investigated the scope and limitations of this new MCR. First, we investigated several α-acidic nitriles including cyanoacetic acid, cyanoacetic acid methyl ester, and several cyanoacetamides. All these reagents reacted smoothly and yielded the expected product in moderate to good yields (**D1–14**). In the case of the cyanoacetic acid, the TEA salt (**D10**) is isolated. We were especially pleased that the cyanoacetamides derived from primary (**D4–9**) and secondary amines (**D3**) reacted satisfactory. This is important because of the great variability of this component. In case with terminal alkyne chain (**D12**) or 3-indoyl function group (**D13**), reactions are fine, also. Next, we investigated the aldehyde component. We found that several substituted benzaldehydes including unprotected salicylaldehyde (**D9**), electron-poor fluoro-benzaldehyde (**D6**), and bulky naphthaldehyde (**D5**) reacted. Also, we were pleased to find that heteroaromatic 2-, 3-, and 4-pyridine carbaldehyde (**D7, D14,** and **D8**) resulted in the projected product. Unfortunately, we also found that aliphatic aldehydes do not react accordingly; however, difficult-to-separate mixtures of products resulted. For the aminoacetophenone sulfonamide component, we tried only the parent compound and the 4-bromo derivative, which expectedly reacted both accordingly. Put conditions into scheme above table (Table 1).

A possible reaction mechanism is proposed in Scheme 2. The most acidic component in the mixture, the cyanomethylene component (**A**), adds onto the benzaldehyde carbonyl (**B**) and yields the α,β-unsaturated nitrile (**F**) after dehydration (Knoevenagel condensation). Next, the second most acidic component the sulfonamide (**C**) undergoes a Michael-type addition acting as a *C*-nucleophile. The remaining sulfonamide is deprotonated and intramolecularly attacks the nitrile to yield after tautomerization the pyrrolidine (**E**), acting as an *N*-nucleophile. Finally, sulfinic acid abstraction affords the final 2-aminopyrrole (**D**). This mechanism is supported by the recent



Scheme 2: Proposed reaction mechanism of the 3-CR.



Scheme 3: A pyrrolidone **E1** can be converted into the 2-aminopyrrole **D11** using forced conditions, pointing to the pyrrolidone as an intermediate of the new MCR.

report on the isolation of intermediate *N*-sulfonamide pyrrolidine (**E1**) by another group by reacting cyanoacetamide, aldehydes, and aminoacetophenone sulfonamide in ethanol at 50 °C in the presence of TEA as a base (20). We repeated this work and prepared compound (**E1**) and indeed we found that refluxing this isolated intermediate in TFE in the presence of triethylamine yields the expected 2-aminopyrrole (**D11**). Thus, slightly enhancing the temperature of the reaction and switching from solvent ethanol to trifluorethanol leads to a new hitherto unknown scaffold class (Scheme 3).

In summary, we have described a new MCR of aminoacetophenone sulfonamide, (hetero)-benzaldehydes, and malonodinitrile or cyanoacetic acid derivatives. This unprecedented reaction gives efficient access to the new scaffold class of 2-amino-5-ketoarylpyrroles. Especially pleasing is the convenient work up, simply by filtration, to yield NMR pure samples. Current efforts in our laboratories are directed toward biological evaluation of this interesting new class of compounds.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Data S1. Details for the preparation of all new compounds, including ^{1}H, ^{13}C spectral data.

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