Tetrahedron Letters 53 (2012) 4743–4746

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Synthesis of novel pyrazole derivatives incorporating one dicarba-*closo*-dodecaborane unit

Naiara Vázquez, Vanessa Gómez-Vallejo, Jordi Llop *

Radiochemistry Department, CIC biomaGUNE, Paseo Miramón 182, San Sebastián 20009, Spain

ARTICLE INFO

Article history:
Received 16 May 2012
Revised 20 June 2012
Accepted 26 June 2012
Available online 2 July 2012

Keywords:
CB1 receptor
Carborane
Pyrazole

ABSTRACT

Boron clusters, and especially dicarba-*closo*-dodecaboranes, can be used as hydrophobic pharmacophores in the design of new drugs. In the current letter, analogs of the CB1 receptor inverse agonist Rimonabant incorporating a carborane cage (either *ortho*- or *meta*-carborane) have been synthesized in moderate yields and their structure has been elucidated by means of ^{1}H NMR, ^{13}C NMR, ^{11}B NMR, and HPLC-MS.

The icosahedral carboranes (dicarba-*closo*-dodecaboranes) are molecules with characteristic and unique structural and chemical properties, that is, rigid geometry, rich derivative chemistry, thermal and chemical stability, and exceptional hydrophobic character. Due to this fact, they have attracted special interest and derivatives with potential application in the fields of heat-stable polymers,[1] non-linear optical,[2] electronic materials,[3] and medicine[4] have been developed for years. Within the latter application, most of the efforts have been directed toward the development of boron neutron capture therapy (BNCT) agents by attaching the carborane clusters to targeting moieties, that is, carbohydrates,[5] porphyrins,[6] or nucleosides.[7] However, Endo and co-workers[8] showed that 1,2- and 1,7-dicarba-*closo*-dodecaborane (*o*- and *m*-carborane) can also act as a hydrophobic structure of various biologically active molecules because both their spherical structure and hydrophobic surface facilitate the interaction with hydrophobic residues of the ligand binding pocket of receptors; in this context, they developed a series of 1,7-dicarba-*closo*-carborane (*m*-carborane) derivatives which acted as an ERα antagonist in luciferase reporter gene assay.[8b]

Based on Endo's group approach, we recently developed analogs of D_2 receptor antagonists Raclopride and FLB-457, by replacing the poly-substituted phenyl moieties by different carborane clusters (*o*-carborane, *m*-carborane, and 1-methyl-*o*-carborane, see Fig. 1).[9] In vitro and ex vivo binding assays have been recently performed and will be reported shortly.[10] Although the introduction of the carborane cage led to molecules with strong hydrophobic character with subsequent nonspecific uptake, the incorporation of such carborane structures resulted in good chemical stability under physiologic conditions, especially when 1,7- and 1-methyl-1,2-dicarba-*closo*-dodecaborane clusters were used. Therefore, the incorporation of carborane cages in biologically active molecules, especially in those cases where endogenous ligands already have a significant hydrophobic character, might be appropriate to improve both in vivo behavior and pharmacokinetic properties.

In continuation of our previous work,[9] we present here the synthesis and characterization of new analogs of Rimonabant incorporating different carborane cages in their structure (Compounds **1**–**3**, Fig. 2). Rimonabant, first developed by Sanofi-Aventis,[11] is a CB1 receptor antagonist which has recently been approved in the European Union for the treatment of obesity, and its therapeutic function might be extended to the treatment of addiction[12] and neuropsychiatric disorders.[13] The key binding interaction of Rimonabant is a hydrogen bond formed between its carbonyl group and the Lys192 residue of the CB1 receptor.[14] The binding also involves direct aromatic stacking interactions between its 2,4-dichlorophenyl and the para-chlorophenyl rings with different amino acid sequences of the receptor,[15,16] while the lipophilic piperidinyl moiety fits in a cavity formed by the amino acid residues Val196/Phe170/Leu387 and Met384 (Fig. 3).[16] Structure Activity Relationship (SAR) studies have demonstrated that the 5-substituent of the pyrazole is involved in receptor recognition and antagonism and that a 2,4-dichloro-substituted phenyl ring at the pyrazole 1-position is preferred for affinity as well as for the activity.[14] Additionally, replacement of the amino piperidinyl substituent by alkyl amides, ethers, ketones, alcohols, or alkanes results mostly in decreased affinity, while replacement by pentyl or heptyl chain gave the compounds agonistic properties. These results suggest that the structural and chemical properties of the substituent at the 3 posi-

* Corresponding author.
E-mail address: jllop@cicbiomagune.es (J. Llop).

0040-4039/$ - see front matter © 2012 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tetlet.2012.06.113

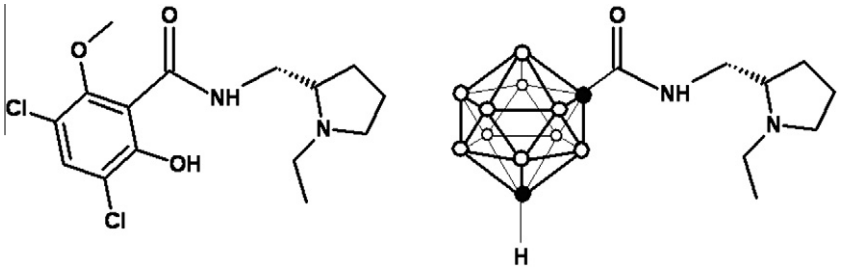


Figure 1. Chemical structures of Raclopride (left) and its analog containing one 1,7-dicarba-*closo*-dodecaborane unit (right). ○ stands for BH, ● stands for C.

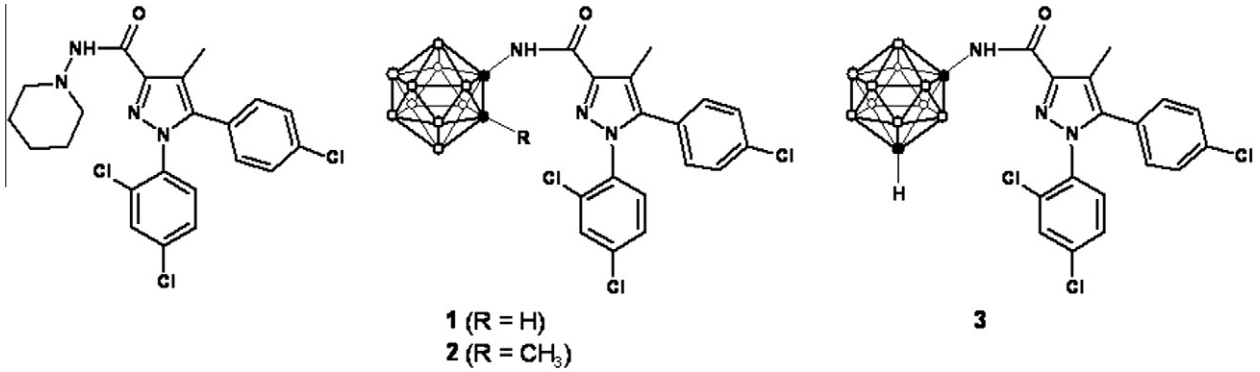


Figure 2. Chemical structure of the CB1 receptor antagonist Rimonabant (left) and analogs incorporating one *o*-carborane cage and one *m*-carborane cage. ○ stands for BH, ● stands for C.

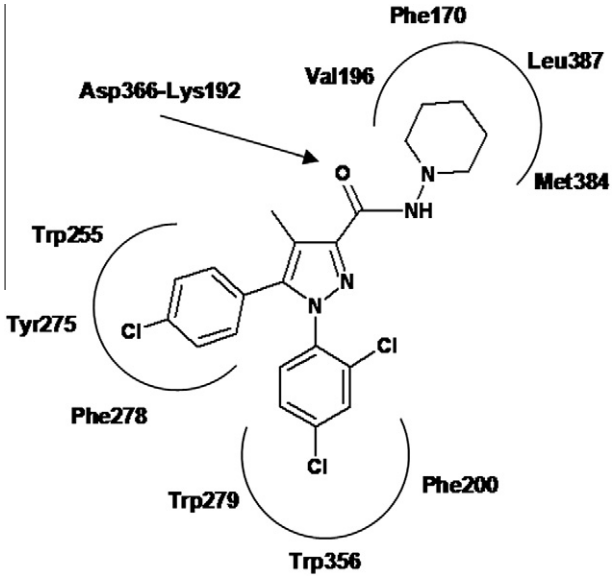


Figure 3. Putative interaction of Rimonabant with amino acid sequences in CB1 receptors.

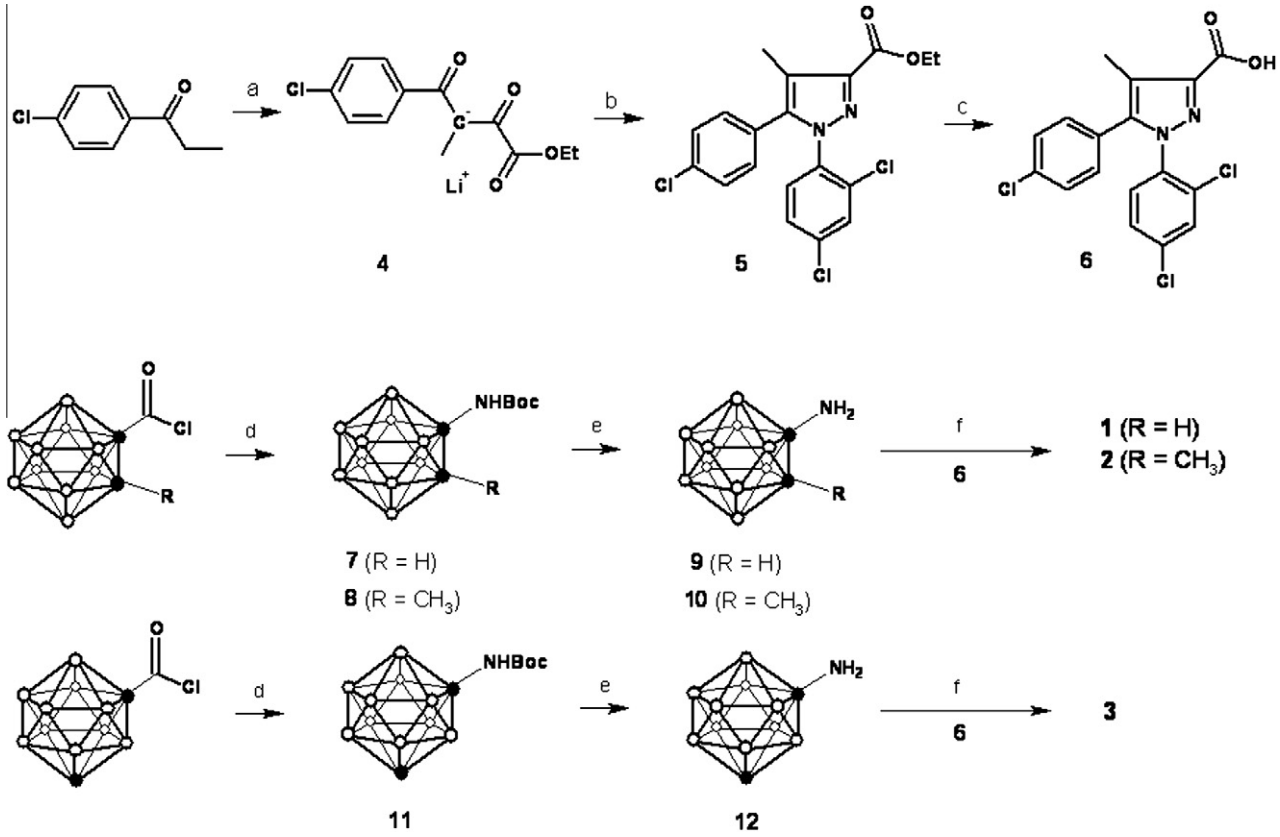
tion of the pyrazole ring have an important effect both in the affinity and the activity of the drug.[17] Thus, in the present work we decided to incorporate the carborane moiety in substitution of the piperidine group, while respecting all other substructures. The carborane cage has a rotating volume similar to the phenyl group; therefore, its fitting into the cavity formed by the amino acid residues Val196/Phe170/Leu387 and Met384 can be anticipated. Moreover, carborane may show greater resistance to metabolism than the replaced piperidinyl ring, which has been shown to be the exclusive region of metabolism of Rimonabant in vitro[18] and in vivo.[18,19]

The general synthetic strategy for the synthesis of Rimonabant analogs (**1**–**3**) is shown in Scheme 1. The synthesis was carried out by condensation of **6** with the amino derivatives of the carborane structures (**9**, **10,** and **12**, respectively).

Compound **6** was prepared following the method reported by Pertwee and co-workers[20] (Scheme 1); briefly: 4-chloropropiophenone was reacted with diethyl oxalate in dry diethyl ether using lithium bis(trimethylsilyl)amide (LiHMDS) as a base yielding the lithium salt of the enolate (**4**), which was further reacted with the substituted phenylhydrazine in ethanol. After centrifugation, the isolated solid was refluxed with acetic acid. After quenching the reaction, the extracted fraction (ethyl acetate, 3 × 40 mL) was evaporated and purified by flash chromatography to obtain **5** in 20% overall yield. Compound **5** was hydrolyzed with LiOH/water to give **6** in quantitative yield.

The synthesis of the primary amines **9**, **10**, and **12** was carried out following the method reported by Washburne and Peterson (Scheme 1).[21] Acid chlorides (prepared according to the method reported by Kahl and co-workers)[22] were reacted with trimethylsilyl azide in toluene to yield the corresponding isocyanates which, after treatment with *tert*-butyl alcohol, yielded the protected amines **7**, **8**, and **11** via Curtius rearrangement in 34%, 11%, and 36% overall yields, respectively. A second strategy, based on the isolation of the isocyanate species and further reaction with LiOH in THF/water was assayed; however, yields mentioned above could not be improved and the strategy was discarded.

Different experimental conditions were assayed for the preparation of Rimonabant analogs **1**–**3**. First attempts were performed using dichloromethane as a solvent and triethylamine as a base, with addition of $SOCl_2$ for the in situ formation of the corresponding acid chlorides, but no desired product was detected in the reaction mixture in any case. Identical results were obtained when diisopropylethylamine was used as a base. Activation of the carboxylic acid using *N,N′*- diisopropylcarbodiimide (DIC) in the presence of additives such as *N*-hydroxysuccinimide (NHS) or 1-hydroxy-7-azabenzotriazole (HOAT) was also unsuccessful when



Scheme 1. Synthesis of compounds **1–3**. Reagents and conditions: (a) LiHMDS/Et_2O anhydrous/−78 °C, then diethyl oxalate, rt. (b) 2,4-Dichlorophenylhidrazine hydrochloride/EtOH; (c) LiOH in THF/H_2O, 0–25 °C. (d) $TMSN_3$, toluene, reflux, then ^tBuOH, reflux; (e) TFA, DCM, 0–25 °C; (f) $SOCl_2$ on the acid, then addition of **9**, **10**, or **12** in toluene, 150 °C, 50 min, microwave.

reactions were performed at room temperature. Based on the literature data,[23] microwave heating (150 °C, 50 min) was applied using toluene as a solvent and compound **1** could be synthesized and isolated in 43% yield. The same procedure was applied to the preparation of compounds **2** and **3**, which could be also synthesized and isolated in 10% and 33% yields, respectively. Shorter reaction times offered lower yields in all cases; although major impurities were identified as unreacted amines (**9**, **10** and **12**) and the hydrolyzed form of acid chloride **6**, increasing reaction time up to 120 min did not lead to significantly improved yields. The moderate yields obtained can be attributed to the low nucleophilic character of the amino group attached to the carborane cage, which is due to the strong electron-withdrawing effect of the carboranyl group.[24] Interestingly, the lowest chemical yield corresponds to compound **2**, which might be interpreted as a result of the steric hindrance due to the presence of the methyl group on one of the carbon atoms of the carborane cage.

$\{^1H–^{11}B\}$ NMR, ^{13}C NMR and $\{^{11}B\text{-}^1H\}$ NMR, and Electrospray Mass Spectrometry measurements confirmed the chemical structure of compounds **1–3**.[25,26] Evaluation of the binding affinity and the agonist/antagonist properties of the newly developed compounds are out of the scope of the present work.

In summary, we have designed and synthesized three new analogs of the CB1 receptor antagonist Rimonabant by replacing the piperidinyl substituent by 1,2-dicarba-*closo*-dodecaborane (**1**), 1-methyl-1,2-dicarba-*closo*-dodecaborane (**2**), and 1,7-dicarba-*closo*-dodecaborane (**3**) in 43%, 10%, and 33% yields. The piperidinyl moiety in Rimonabant is supposed to interact with CB1 receptors via hydrophobic interaction with the cavity formed by the amino acid residues Val196/Phe170/Leu387 and Met384. Thus, the introduction of the carborane structures, which have significant hydrophobic character, might lead to improved binding properties and in vivo stability as well as modulation of the agonist/antagonist character of the resulting compounds.

Acknowledgments

The authors would like to thank Dr. Javier Calvo for providing mass spectroscopy data as well as the Departamento de Industria, Comercio y Turismo of the Basque Government and the Ministerio de Ciencia e Innovación (Grant number CTQ2009-08810) for financial support.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.06.113.

References and notes

1. Schoberl, U.; Magnera, T. F.; Harrison, R. M.; Fleischer, F.; Pflug, J. L.; Schwab, P. F. H.; Meng, X.; Lipiak, D.; Noll, B. C.; Allured, V. S.; Rudalevige, T.; Lee, S.; Michl, J. *J. Am. Chem. Soc.* **1997**, *119*, 3907–3917.
2. Murphy, D. M.; Mingos, D. M. P.; Haggit, J. L.; Powell, H. R.; Westcott, S. A.; Marder, T. B.; Taylor, N. J.; Kanis, D. R. *J. Mater. Chem.* **1993**, *3*, 139–148.
3. Chetcuti, P. A.; Hofherr, W.; Liegard, A.; Rihs, G.; Rist, G.; Keller, H.; Zech, D. *Organometallics* **1995**, *14*, 666–675.
4. Valliant, J. F.; Guenther, K. J.; King, A. S.; Morel, P.; Schaffer, P.; Sogbein, O. O.; Stephenson, K. A. *Coord. Chem. Rev.* **2002**, *232*, 173–230.
5. (a) Maurer, J. L.; Serino, A. J.; Hawthorne, M. F. *Organometallics* **1988**, *7*, 2519; (b) Giovenzana, G. B.; Lay, L.; Monti, D.; Palmisano, G.; Panza, L. *Tetrahedron* **1999**, *55*, 14123; (c) Sneath, R. L.; Wright, J. E.; Soloway, A. H.; O'Keefe, S. M.; Dey, A. S.; Smolnycki, W. D. *J. Med. Chem.* **1976**, *19*, 1290.
6. Soloway, A. H.; Tjarks, W.; Barnum, A.; Rong, F. G.; Barth, R. F.; Codogni, I. M.; Wilson, J. G. *Chem. Rev.* **1998**, *98*, 1515.
7. (a) Lesnikowski, Z. J.; Shi, J.; Schinazi, R. F. *J. Organomet. Chem.* **1999**, *581*, 156; (b) Hurwitz, S. J.; Ma, L.; Eleuteri, A.; Wright, J.; Moravek, J.; Schinazi, R. F.

Nucleosides Nucleotides Nucleic Acids **2000**, *19*, 691; (c) Schinazi, R. F.; Hurwitz, S. J.; Liberman, I.; Juodawlkis, A. S.; Tharnish, P.; Shi, J.; Liotta, D. C.; Coderre, J. A.; Olson, J. *Clin. Cancer Res.* **2000**, *6*, 725.
8. (a) Endo, Y.; Iijima, T.; Yamakoshi, Y.; Yamaguchi, M.; Fukasawa, H.; Shudo, K. *J. Med. Chem.* **1999**, *42*, 1501–1504; (b) Ogawa, T.; Ohta, K.; Yoshimi, T.; Yamazaki, H.; Suzuki, T.; Ohta, S.; Endo, Y. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 3943–3946.
9. Vázquez, N.; Gómez-Vallejo, V.; Calvo, J.; Padro, D.; Llop, J. *Tetrahedron. Lett.* **2011**, *52*, 615–618.
10. Gómez-Vallejo, V.; Vázquez, N.; San Sebastian, E.; Martín, A.; Llop, *J. Bioorg. Med. Chem.* submitted for publication.
11. Rinaldi-Carmona, M.; Barth, F.; Heaulme, M.; Shire, D.; Calandra, B.; Congy, C.; Martinez, S.; Maruani, J.; Neliat, G.; Caput, D. *FEBS Lett.* **1994**, *350*, 240–244.
12. De Vries, T. J.; Schoffelmeer, A. N. *Trends Pharmacol. Sci.* **2005**, *26*, 420–426.
13. (a) Witkin, J. M.; Tzavara, E. T.; Nomikos, G. G. *Behav. Pharmacol.* **2005**, *16*, 315–331; (b) Witkin, J. M.; Tzavara, E. T.; Davis, R. J.; Li, X.; Nomikos, G. G. *Trends Pharmacol. Sci.* **2005**, *26*, 609–617; (c) Vinod, K. Y.; Arango, V.; Xie, S.; Kassir, S. A.; Mann, J. J.; Cooper, T. B.; Hungund, B. L. *Biol. Psychiatry* **2005**, *57*, 480–486.
14. Lange Jos, H. M.; Kruse Chris, G. *Drug Discov. Today* **2005**, *10*. 693-70.
15. McAllister, S. D.; Rizvi, G.; AnaviGoffer, S.; Hurst, D. P.; Barnett-Norris, J.; Lynch, D. L.; Reggio, P. H.; Abood, M. E. *J. Med. Chem.* **2003**, *46*, 5139–5152.
16. Lange, J. H. M.; Coolen, H. K. A. C.; van Stuivenberg, H. H.; Dijksman, J. A. R.; Herremans, A. H. J.; Ronken, E.; Keizer, H. G.; Tipker, K.; McCreary, A. C.; Veerman, W.; Wals, H. C.; Stork, B.; Verveer, P. C.; den Hartog, A. P.; de Jong, N. M. J.; Adolfs, J. P.; Hoogendoorn, J.; Kruse, C. G. *J. Med. Chem.* **2004**, *47*, 627–643.
17. Mucciolini, G. G.; Lambert, D. M. *Curr. Med. Chem.* **2005**, *12*, 1361–13-94.
18. Zhang, Q.; Ma, P.; Wang, W.; Cole, R. B.; Wang, G. *Drug Metab. Dispos.* **2005**, *33*(4), 508–517.
19. Albert, J. J.; Li, W.; Behnia, K.; Zhang, L. M.; Johnghar, S.; Humphreys, W. G.; Zadjura, L.; Davis, C. D.; Santone, K. S.; Hunag, S.; Liu, X.; Kang, L.; Carlson, K. E.; Wu, S. T.; Shu, Y.-Z. *Drug Metab. Rev.* **2003**, *35*(Suppl. 2), 38.
20. Lan, R.; Riu, Q.; Fan, P.; Lin, S.; Fernando, R. R.; McCallion, D.; Pertwee, R.; Makriyannis, A. *J. Med. Chem.* **1999**, *42*, 769–776.
21. Washburne, S. S.; Peterson, W. R., Jr. *Synth. Commun.* **1972**, *2*, 1733–1736.
22. (a) Kahl, S. B.; Kasar, R. A. *J. Am. Chem. Soc.* **1996**, *118*, 1223–1224; (b) Kasar, R. A.; Knudsen, G. M.; Kahl, S. B. *Inorg. Chem.* **1999**, *38*, 2936–2940.
23. Endo, Y.; Yaguchi, K.; Kawachi, E.; Kagechika, H. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1733–1736.
24. Kalinin, V. N.; Ol'shevskaya, V. A. *Russ. Chem. Bull., Int. Ed.* **2008**, *57*(4), 815–836.
25. Compound **1**: ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.12–2.70 (m, 10H, B*H*), 2.26 (s, 3H, CH_3), 5.01 (s, 1H, C*H*-carborane), 6.97–7.02 (d, J = 10 Hz, 2H, Ar), 7.21–7.38 (m, 5H, Ar), 7.83 (s, 1H, CON*H*); ^{13}C NMR ($CDCl_3$, 125.77 MHz): δ 9.47, 60.59, 78.91, 118.85, 126.67, 128.21, 129.25, 129.31, 130.97, 135.58, 136.69, 142.81, 144.14, 160.63; ^{11}B NMR ($CDCl_3$, 160.46 MHz, decoupled): δ -13.79, -10.88, -7.08, -3.90; HRMS (ESI): m/z calculated for $C_{19}H_{22}B_{10}Cl_3N_3ONa$: 545.1722 $[M+Na]^+$; found: 545.1721.
Compound **2**: ^{1}H NMR ($CDCl_3$, 500MHz): δ 2.02-2.59 (m, 10H, B*H*), 2.00 (s, 3H, CH_3-C(carborane)), 2.33 (s, 3H, CH_3), 7.02–7.43 (m, 7H, Ar), 8.02 (s, 1H, CON*H*); ^{13}C NMR ($CDCl_3$, 125.77MHz): δ 9.56, 22.55, 79.01, 82.48, 119.10, 126.74, 128.20, 129.29, 130.61, 131.01, 135.63, 136.68, 143.04, 144.21, 160.47; ^{11}B NMR ($CDCl_3$, 160.46MHz, decoupled): δ −11.75, −10.16, −6.12; HRMS (ESI): m/z calculated for $C_{20}H_{24}B_{10}Cl_3N_3ONa$: 559.1879 $[M+Na]^+$; found: 559.1916.
Compound **3**: ^{1}H NMR ($CDCl_3$, 500MHz): δ 2.02–2.62 (m, 10H, B*H*), 2.32 (s, 3H, CH_3), 2.94 (s, 1H, C*H*-carborane), 7.00–8.13 (m, 7H, Ar); ^{13}C NMR ($CDCl_3$, 125.77MHz): δ 9.58, 53.35, 80.00, 118.64, 119.75, 127.01, 127.41, 128.14, 129.18, 130.56, 131.01, 131.11, 143.51, 143.77, 149.57, 160.20, 189.50; ^{11}B NMR ($CDCl_3$, 160.46MHz, decoupled): δ −15.04, −12.40, −10.67, −3.79; HRMS (ESI): m/z calculated for $C_{19}H_{21}B_{10}Cl_3N_3O$: 521.1746 $[M-H]-$; found: 521.1744.
26. UPLC/ESI-MS analyses were performed using an ACQUITY UPLC separation module coupled to a LCT TOF premier XE mass spectrometer (Waters, Manchester, UK). An Acquity BEH C18 column (1.7 μm, 5 mm, 2.1 mm) was used as the stationary phase. The elution buffers were A (methanol) and B (0.1% formic acid aqueous solution). The column was eluted with a linear gradient: t = 0 min, 95% B; t = 3 min, 1% B; t = 4 min, 1% B; t = 5 min, 95% B. Total run was 5 min, injection volume was 5 μL and the flow rate was 600 μL/min. The detection was carried out in positive mode, monitoring the most abundant isotope peaks from the mass spectra ($M-H^+$).